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BRUCE JANCIN/MDEDGE NEWS

Dr. Fernando Dominguez said, "It was essential to use objectively measured sleep variables, because they showed huge disparity with patients' self-reports on sleep questionnaires."

Sleep: The new frontier in cardiovascular prevention

BY BRUCE JANCIN
MDedge News

MUNICH – Getting less than 6 hours of sleep nightly on a regular basis or waking up multiple times was independently associated with increased risk of subclinical atherosclerosis in the Spanish PESA study, Fernando Dominguez, MD, reported at the annual congress of the European Society of Cardiology.

Moreover, a graded response was evident in PESA (Progression of Early Subclinical Atherosclerosis): The more times an individual typically awoke per night, the greater the number of atherosclerotic carotid or femoral artery territories documented on three-dimensional vascular ul-

trasound, added Dr. Dominguez of the Spanish National Center for Cardiovascular Research in Madrid.

"These findings show that sleep is associated with cardiovascular health and suggest that the modification of abnormal sleep patterns may contribute to the reduction of burden of cardiovascular diseases," the cardiologist said.

The cross-sectional PESA study, whose principal investigator was Valentin Fuster, MD, PhD, included 3,974 middle-aged Madrid bank employees free of known heart disease or history of stroke who wore a waistband activity monitor for a week to record sleep quantity and quality. They also underwent three-di-

SLEEP // *continued on page 7*

Cigarette smoking drops to historic low

BY RICHARD FRANKI
MDedge News

The prevalence of cigarette smoking among adults was down to 14% in 2017, the lowest level recorded since monitoring began in 1965, according to the Centers for Disease Control and Prevention.

"This new all-time low in cigarette smoking among U.S. adults is a tremendous public health accomplishment, and it demonstrates the importance of continued proven strategies to reduce smoking," CDC Director Robert Redfield said in a written statement.

In 2017, 19.3% of adults aged 18 years and older – approximately 47.4 million Americans – reported current use of some type of tobacco product, and current use of combustible tobacco was 16.7%, Teresa W. Wang, PhD, of the CDC's National Center for Chronic Disease Prevention and Health Promotion, and her associates reported in the Morbidity and Mortality Weekly Report. Current use was defined as use every day or some days, with an added requirement of at least 100 cigarettes in a lifetime added for cigarette smokers.

Data from the National Health Interview Survey
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INSIDE HIGHLIGHT



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Use of ECMO in the management of influenza-associated ARDS

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FDA approves return of Primatene Mist

BY MICHELE G. SULLIVAN

MDedge News

After a long absence, Primatene Mist, an over-the-counter asthma inhaler removed from

the market in 2011, is being reintroduced in a metered-dose inhaler with a new, environmentally friendly propellant.

The inhaler's comeback may prove as controversial as its re-

moval. Respiratory medicine associations have taken issue with the Food and Drug Administration's decision, warning patients that asthma is not a "do-it-yourself" disease that can be managed with

over-the-counter medications.

The American College of Allergy, Asthma, and Immunology, American College of Chest Physicians, American Lung Association, American Thoracic Society, and

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the American Association of Asthma Educators have each individually protested the decision, and together sent a joint resolution to FDA decrying it. At the core of their protest are the facts that epinephrine is a symptomatic, not therapeutic, asthma treatment and that racemic epinephrine is not a recommended asthma treatment

under the National Institutes of Health's "Guidelines for the Diagnosis and Management of Asthma."

The inhaler was pulled from sales as part of an international pact to reduce ozone-depleting substances. The 1989 Montreal Protocol of Substances that Deplete the Ozone Layer and the Clean Air Act of 1990

targeted chlorofluorocarbons among those substances, and epinephrine inhalers that contained CFCs were phased out.

The new Primatene Mist HFA (Amphastar Pharmaceuticals) contains hydrofluoroalkane (HFA) propellants, which are permitted under current international and U.S. law. This puts Primatene in the

same category with other inhalers, including albuterol and levalbuterol, which also use HFAs as propellants. Each dose delivers 125 mcg of epinephrine.

The inhaler itself has also been redesigned, according to Theresa Michele, MD, director of the FDA's Division of Nonprescription Drug Products in the Center for Drug Evaluation and Research. The active ingredient is still epinephrine, albeit a smaller dose than found in the original 200-mcg mist. However, the inhaler needs to be activated before first use and cleaned every day after use to prevent a medication buildup. Like other metered-dose inhalers, it requires a priming spray before the inhalation dose, Dr. Michele noted in her online column.

"The inhaler also needs to be shaken and then sprayed once into the air before each use. It may seem strange to shake and spray the inhaler into the air each time before using it. But these two steps are critical to ensure that the medicine is properly mixed before each dose," Dr. Michele wrote.

A public statement by FDA Commissioner Scott Gottlieb, MD, and Janet Woodcock, MD, director of the Center for Drug Evaluation and Research, asserted that the inhaler fills a clinical gap for patients with mild to moderate intermittent asthma.

"The scientific information we reviewed to approve the new version of OTC Primatene Mist shows there is a narrow population of those diagnosed with asthma that may benefit from having access to this type of OTC asthma inhaler. But the product has certain cautions. Making sure that patients can understand and apply the instructions for use was a critical consideration for the FDA.

The new product is only appropriate for those with a diagnosis of mild, intermittent asthma. Patients with more severe asthma should not rely on it. Instead, they should be working with their health care provider to ensure an appropriate treatment plan for their condition."

Before this approval, Amphastar had unsuccessfully brought the reformulated Primatene before FDA several times. The move to finally reinstate it comes after a long, and sometimes contentious, debate among patients and FDA's Nonprescription Drugs and Pulmonary-Allergy Drugs advisory committee. A quick Internet or Facebook search brings up dozens of stories from patients who say they effectively managed their mild to moderate asthma

Continued on following page

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for years with Primatene. Typically, the stories describe changing to prescription asthma medications that, for some, run into the hundreds of dollars per month.

Supporters often negatively compare decades of using the inexpensive Primatene with no ill effects to their recent experiences using prescription corticosteroid inhalers.

It was 4 years ago when Amphastar first appeared before the advisory committee with the reformulated inhaler and positive safety and efficacy data. Although agreeing with the efficacy data, the advisory committee voted against approval, because some felt that asthma should always be managed by a physician; an OTC bronchodilator encouraged self-medicating and discouraged patients from seeking medical care, they said. "On the one hand, it has been stated that a quick-relief medication available OTC is needed for use in low-income, elderly, and uninsured individuals who might otherwise not have access to treatment or be able to see a health care practitioner," FDA documents noted. "In contrast, there is also a concern that because asthma is a potentially life-threatening condition that should be diagnosed and treated by a health care professional, availability of an OTC bronchodilator product may discourage consumers from seeking appropriate care, resulting in worse asthma outcomes."

Two years later, the company received another blow to Primatene program. FDA's Complete Response Letter required Amphastar to make additional changes to the packaging and run a consumer product safety study, intended to show that people could learn to use the metered-dose

inhaler correctly.

In Amphastar's 2018 first-quarter report, however, company CEO Jack Zhang, PhD, finally shared some good news. "We are pleased to announce that we have resubmitted our NDA for Primatene Mist after receiving good results from our recent human factors study. While we don't have a Prescription Free User Drug Act [PDUFA] date yet, we plan to begin producing inventory in preparation for a launch."

That day arrived on Nov. 8, when the PDUFA was granted. In their public letter, Dr. Gottlieb and Dr. Woodcock acknowledged the long and difficult approval path and offered reassurance that Primatene is safe and effective.

He said, "For the right patient, our analysis of the data, including new information that was developed since this product was previously on the market, shows that there are no serious safety concerns when Primatene Mist is used as directed. The product is appropriate for mild symptoms of intermittent asthma, however, even patients with mild asthma can have severe exacerbations – so it's still important to consult a health care provider about appropriate care and have their condition reassessed. And, of course, all patients who experience severe exacerbations should go to the emergency room right away."

The product is intended for the temporary relief of mild symptoms of intermittent asthma (wheezing, tightness of chest, shortness of breath) in patients aged 12 years and older. It should not be considered a replacement for prescription asthma medications. It should be available in stores early next year.

msullivan@mdedge.com

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

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CHEST STATEMENT ON FDA DECISION

The American College of Chest Physicians (CHEST) is disappointed with the FDA's decision to approve over-the-counter epinephrine (Primatene® Mist HFA) for the treatment of asthma. CHEST is a nonprofit organization dedicated to advancing best patient outcomes. Our membership of more than 19,000 members from around the world provides patient care in pulmonary, critical care, and sleep medicine.

Asthma is a serious and chronic condition with associated high health-care burden. Care for ALL patients with asthma should be under the guidance of a health-care provider. The majority of asthma patients requires treatment with a controller medication, which is only available by prescription. Frequent rescue inhaler use has been associated with increased morbidity and mortality. Over the counter availability of a reliever medication like Primatene Mist can endanger a patient's wellbeing by providing temporary relief in symptoms, resulting in delay in seeking medical care.

Studies needed on long-term impact of sleep deficit // continued from page 1

mensional vascular ultrasound and measurement of coronary artery calcium.

PESA was one of several large studies presented at the meeting that focused on deviations from normal sleep as a marker for increased risk of cardiovascular disease and/or mortality. Of note, however, PESA was the only one to use activity monitoring technology to track sleep.

“It was essential to use objectively measured sleep variables, because they showed huge disparity with patients’ self-reports on sleep questionnaires,” Dr. Dominguez said.

Indeed, while 10.7% of PESA participants self-reported sleeping less than 6 hours per night on the Sleep Habits Questionnaire, actigraphy showed the true rate was 27.1%.

Based on actigraphic findings, subjects were divided into tertiles based upon average hours of sleep per night, ranging from less than 6 to more than 8. They were also grouped in quintiles based upon their extent of fragmented sleep.

Subjects with short sleep were significantly older and more likely to have high blood pressure, a higher body mass index, and metabolic syndrome than those who averaged 7-8 hours of sleep. Individuals in the top quintile for sleep awakening were older and had higher prevalences of smoking and hypertension than those in the lowest quintile.

In multivariate analyses adjusted for these differences as well as for physical activity, depression, obstructive sleep apnea, daily calorie consumption, alcohol intake, and other potential confounders, subjects who slept less than 6 hours per night had a 27% greater volume of

noncoronary plaque than those who slept 7-8 hours. They also had 21% more vascular territories laden with subclinical atherosclerosis. The risk of subclinical noncoronary atherosclerosis was greater among women who averaged less than 6 hours of sleep per night, representing a 48% relative risk increase in plaque volume, versus 21% in men.

At the other extreme, women who slept more than 8 hours per



Moa Bengtsson

night had an 83% increased plaque volume, while men who slept that much had no increase in risk, compared with men who slept for 7-8 hours.

Subjects in the top quintile for sleep fragmentation had 34% more vascular territories affected by atherosclerosis than those in the lowest quintile. Their noncoronary plaque burden was 23% greater as well.

Meta-analysis has 11 studies

Epameinondas Fountas, MD, of the Onassis Cardiac Surgery Center in Athens, presented a meta-analysis

of 11 prospective studies of the relationship between daily sleep duration and cardiovascular disease morbidity and mortality published within the past 5 years, reflecting burgeoning interest in this hot-but-ton topic. Collectively, the meta-analysis totaled 1,000,541 adults without baseline cardiovascular disease who were followed for an average of 9.3 years.

In an analysis adjusted for numerous known cardiovascular risk factors, the Greek investigators found that short sleep duration as defined by a self-reported average of less than 6 hours per night was independently associated with a statistically significant 11% increase in the risk of diagnosis of fatal or nonfatal cardiovascular disease, compared with individuals who averaged 6-8 hours nightly. Moreover, those who averaged more than 8 hours of

sleep per night were also at risk: They averaged a 32% increased risk in fatal or nonfatal cardiovascular events compared to normal 6- to 8-hour sleepers. Thus, 6-8 hours of sleep per night appears to be the sweet spot in terms of cardioprotection.

Numerous investigators have highlighted the pathophysiologic changes related to sleep deprivation that likely boost cardiovascular risk. These include activation of the sympathetic nervous system, increased inflammation, and disrupted glucose metabolism, he noted.

Swedes weigh in

Moa Bengtsson, a combined medical/PhD student at the University of Gothenburg (Sweden), presented a prospective study of 798 men who were 50 years old in 1993, when they underwent a physical examination and completed extensive lifestyle questionnaires that included average self-reported sleep duration. Among the 759 men still available for evaluation after 21 years, or nearly 15,000 person-years of follow-up, those who reported sleeping an average of 5 hours or less per night back at age 50 were 93% more likely to have experienced a major cardiovascular event by age 71 – acute MI, stroke, coronary revascularization, heart failure hospitalization, or cardiovascular death – compared with those who averaged 7-8 hours of shut-eye.

The short sleepers had a higher prevalence of obesity, diabetes, hypertension, smoking, and physical inactivity than the men who slept 7-8 hours per night.

Like the other investigators, she noted that the studies presented at the meeting, despite their extensive adjustments for potential confounders, don’t prove a direct causal relationship between short sleep and increased cardiovascular risk. An informative next step in research, albeit a challenging one, would be to show whether improved long-term sleep habits favorably alter cardiovascular risk.

All three study investigators reported having no financial conflicts regarding their research, which was conducted free of commercial support.

bjancin@mdedge.com

Tobacco products have evolved // continued from page 1

vey showed that from 2016 to 2017 current use declined for any tobacco product, any combustible tobacco product, cigarettes, smokeless tobacco, and the combination of two or more tobacco products. The most common combination in 2017 was cigarettes and e-cigarettes, which was reported by 30.1% of the 9 million adults who used more than one product.

Prevalence of current tobacco use was higher among men than women (24.8% vs. 14.2%), and adults aged 25-44 years (22.5%) had the highest level by age, followed by those aged 45-64 years (21.3%), 18-24 years (18.3%), and 65 years or older (11%). Use by race/ethnicity was highest among American Indian/Alaska Natives (29.8%), with the Midwest

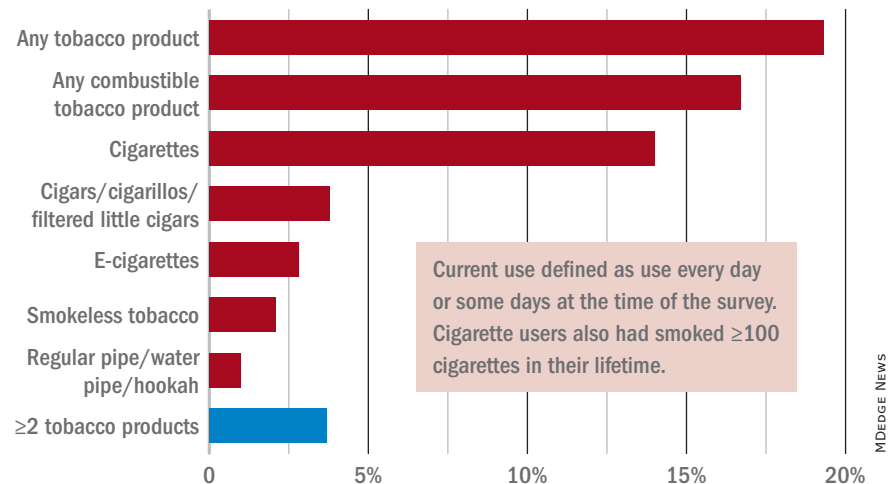
putting up the highest prevalence by region at 23.5%, they said.

“Although cigarette smoking among U.S. adults has declined considerably, tobacco products have evolved in recent years to include various combustible, noncombustible, and electronic products,” the authors wrote. “Implementation of evidence-based tobacco control interventions that address the diversity of tobacco products used by U.S. adults, in coordination with regulation of tobacco product manufacturing, marketing, and sales, can reduce tobacco-related disease and death.”

rfranki@mdedge.com

SOURCE: Wang TW et al. MMWR. 2018 Nov 9;67(44):1225-32.

Prevalence of current tobacco product use among adults, 2017



Note: Based on data from the National Health Interview Survey.

Source: MMWR. 2018 Nov 9;67(44):1225-32

PIONEER-HF called practice changing for acute HF

BY BRUCE JANCIN

MDedge News

CHICAGO – Initiation of angiotensin-neprilysin inhibition using sacubitril/valsartan during hospitalization for acute decompensated heart failure, instead of relying upon enalapril, resulted in a substantially greater reduction in N-terminal of the prohormone brain natriuretic peptide concentration and a markedly lower rate of rehospitalization with no safety downside in the PIONEER-HF trial, Eric J. Velazquez, MD, reported at the American Heart Association scientific sessions.

“We believe these results have clinical implications that support the in-hospital initiation of sacubitril/valsartan in stabilized patients with acute decompensated heart failure and reduced ejection fraction irrespective of prior ACE inhibitor or ARB [angiotensin II receptor blocker] use or prior diagnosis of heart failure,” said Dr. Velazquez, a professor of medicine and chief of the section of cardiovascular medicine at Yale University, New Haven, Conn., and physician in chief of the Heart and Vascular Center for the Yale-New Haven Health System.

Sacubitril/valsartan (Entresto) has a class I indication for treatment of symptomatic heart failure with reduced ejection fraction (HFrEF) in the AHA/American College of Cardiology guidelines. This strong recommendation is based largely upon the impressive results of the PARADIGM-HF trial, which in ambulatory outpatients demonstrated a lower risk of cardiovascular mortality or hospitalization for heart failure than enalapril (*N Engl J Med.* 2014 Sep 11;371[11]:993-1004).

However, since patients with acute decompensated heart failure (ADHF) were excluded from PARADIGM-HF, the safety and effectiveness of starting such patients on the drug while hospitalized for acute decompensation was unknown.

PIONEER-HF was carried out to shed light on that issue and thereby address a major unmet need for better treatments for ADHF. Even though this condition accounts for more than 1 million hospitalizations annually in the United States, short-term rehospitalization and mortality rates in affected patients remain unacceptably high at 21% and 12%, respectively. And the standard-of-care treatment – decongestion with intravenous diuret-

ics and hemodynamic support with inotropes and vasodilators – hasn’t changed in nearly half a century, Dr. Velazquez noted.

The trial included 881 patients hospitalized for acute decompensated HFrEF at 129 U.S. centers. The study population was diverse:



Dr. Eric J. Velazquez

36% of participants were black and one-third of subjects had no diagnosis of heart failure prior to their hospitalization. After achieving hemodynamic stabilization, patients were randomized to receive sacubitril/valsartan or enalapril.

Key outcomes

The primary endpoint was change in N-terminal of the prohormone brain natriuretic peptide concentration from baseline to week 8. There was a 25% reduction in the enalapril group and a 45% reduction with sacubitril/valsartan. This translated to a highly significant 29% greater relative risk reduction with sacubitril/valsartan.

More eye-opening was the between-group difference in the prespecified composite clinical endpoint comprising death, rehospitalization for heart failure, implantation of a left ventricular assist device, or listing for heart transplant during the 8-week study.

The rate was 16.8% in the enalapril group and 9.3% with sacubitril/valsartan. This worked out to a 46% relative risk reduction, with a number needed to treat of 13.

The composite result was driven by a 44% reduction in risk of heart failure rehospitalization in the sacubitril/valsartan group: 8.0% versus 13.8%. The sacubitril/valsartan group also had a numerically lower mortality rate: 2.3% versus 3.4%, although the number of fatalities

was small and this 34% relative risk reduction didn’t achieve statistical significance.

Rates of the key safety outcomes – symptomatic hypotension, worsening renal function, hyperkalemia, and angioedema – didn’t differ between the two study arms. Of



Dr. Larry A. Allen

interest, however, all six cases of angioedema in the enalapril group occurred in black patients, while the only case in the sacubitril/valsartan group was in a white patient.

PIONEER-HF treatment strategy

Hemodynamic stabilization as a prelude to randomization to sacubitril/valsartan or enalapril required maintaining a systolic blood pressure of at least 100 mm Hg in the previous 6 hours, with no symptomatic hypotension, intensification of intravenous diuretics, or use of intravenous vasodilators during that time period, and no intravenous inotropes in the previous 24 hours.

Enalapril was titrated to a target dose of 10 mg twice daily. Sacubitril/valsartan was titrated to a target dose of 97/103 mg twice daily. Titration was carried out using an algorithm based upon systolic BP. If the SBP was at least 100 and less than 120 mm Hg at baseline, sacubitril/valsartan was initiated at 24/26 mg twice daily, enalapril at 2.5 mg b.i.d. If the SBP at randomization was 120 mm Hg or higher, the initial dosing was sacubitril/valsartan at 49/51 mm Hg b.i.d. or enalapril at 5 mg b.i.d. Up-titration occurred after 1 week, then biweekly through week 8.

PIONEER in perspective

Discussant Larry A. Allen, MD, a heart failure specialist at the University of Colorado at Denver, Aurora,

predicted that this will be a practice-changing study.

“There has been a need for a study like PIONEER in heart failure,” he observed. While multiple randomized trials have advanced the treatment of ambulatory HFrEF patients, demonstrating benefit for initiation and intensification of treatment with ACE inhibitors, angiotensin II receptor blockers, beta-blockers, and mineralocorticoid receptor antagonists, the treatment of patients with ADHF has remained relatively static, marked by failed trials of once-promising novel agents including tolvaptan, nesiritide, and serelaxin.

“All the data is in ambulatory patients, but the action for the care of heart failure patients actually occurs largely in the hospital. Seventy percent of care provided in the U.S. to patients with heart failure occurs in the hospital setting. These patients are a captive audience at that time, and the transitions from inpatient to outpatient care are fragile,” Dr. Allen said.

He noted that the use of sacubitril/valsartan in routine practice as reflected in national registries has been “extremely low” – less than 15% among eligible patients – despite the drug having been approved more than 3 years ago. One major reason for the low uptake, in his view, is clinical inertia. That should melt away in what he termed “the post-PIONEER world.”

“I think one of the great things about this study is it keeps it simple. We now have a simpler algorithm for inpatient and subsequent outpatient management of heart failure with reduced ejection fraction. It’s easier for us to start with the treatment we want patients to be on, and it’s better for patients, too. Most importantly, this study reinforces the importance and safety of aggressive guideline-directed medical therapy starting from the beginning in most patients,” Dr. Allen said.

The study findings were published simultaneously in the *New England Journal of Medicine* (2018 Nov 11. doi: 10.1056/NEJMoa1812851).

PIONEER-HF was sponsored by Novartis. Dr. Velazquez reported receiving research grants from and serving as a consultant to that company and others. Dr. Allen reported having no financial conflicts.

bjancin@mdedge.com

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Telehealth: States broaden options for providers

BY ALICIA GALLEGOS

MDedge News

More states are expanding their telehealth policies to reach patients, and pulling back on rigid in-person requirements.

Several state Medicaid programs now explicitly allow the home to serve as an originating site for telehealth, with 10 states – Colorado, Delaware, Maryland, Michigan, Minnesota, Montana, New York, Texas, Washington, and Wyoming – adding the home as an approved site since 2016.

In addition, 16 jurisdictions now allow schools to serve as originating sites for telehealth, although some have restrictions about when the sites are acceptable, said Mei Kwong, an attorney and executive director for the Center for Connected Health Policy and the author of the center's Spring 2018 report on telehealth trends.



VERBASKA_STUDIO/THINKSTOCK

At the same time, nearly all states have now dropped Medicaid restrictions that limited reimbursable telehealth services to rural or underserved areas. Colorado, Idaho, Missouri, Nebraska, Nevada, and New Hampshire are the most recent states to remove such geographic restrictions.

“[The expanded locations are] extremely helpful in providing greater access for patients to needed services,” Ms. Kwong said in an interview. “For example, a person who has difficulty leaving his or her home for a physical or other reason, they can get care, [or] a child having a rough time in school, can seek out a mental health counselor while at school.”

More telehealth providers covered

In addition to expanding telehealth sites, states are increasing acceptance for telehealth providers beyond physicians. Most recently, New Jersey enacted a broad telemedicine law that includes doctors, nurses, psychologists, social workers, physician assistants, counselors, respiratory therapists, speech pathologists, and optometrists, among others. The New Jersey law addresses telemedicine practice standards, prescribing, patient consent, privacy, and other requirements for providers.

In addition, more states are carving out telehealth regulations. Since 2016, 11 states have revised or adopted new scope-of-practice restrictions for counselors providing telemedicine, ac-

ording to a state telehealth analysis published in July 2018 by law firm Epstein, Becker, Green.

The developments highlight the rise in more mid- and lower-level providers practicing telemedicine, said Anjali B. Dooley, an attorney and chief legal and compliance officer for Forefront Telecare, a telehealth platform for behavioral health services.

“Increasing scope-of-practice extensions also increases risk if physician extenders are not trained properly in telehealth technology use and protocols,” Ms. Dooley said in an interview. “Providers and provider extenders need to be educated and learned in human factors such as communication, empathy, and etiquette.”

A greater number of nonphysician telemedicine providers is beneficial as long as the providers are adhering to appropriate standards of care and consulting with supervising physicians when necessary, adds Jean R. Sumner, MD, dean of the School of Medicine at Mercer University in Macon, Georgia, and a telemedicine internist.

“The standard should always be equal to an in-person visit,” she said in an interview. “The patient has a right to know who is seeing them, too, to understand [their credentials]. They need to know the person on the telehealth unit is qualified to provide the care.”

Opioid crisis response needed

The need for increased access to mental health care is a primary driver behind state efforts to expand the pool of telemedicine providers, adds Amy Lerman, an attorney at Epstein, Becker, Green and lead author of her firm's report.

“The reason it is important for states to continue expanding the scope of health professionals, other than physicians, who can provide behavioral health telemedicine services, is not only to address an overall nationwide shortage of behavioral health providers, but also to expand access to behavioral health services because a wider range of providers are equipped to provide these services,” she said in an interview.

In the same vein, more states are using telehealth to address the opioid crisis, according to both the Epstein report and the Center for Connected Health Policy analysis.

In September, California enacted a law that would allow Medicaid reimbursement for certified substance use disorder counselors who provide treatment via telehealth. In August, Illinois approved a similar law that mandates reimbursement for behavioral and mental health experts who treat Medicaid patients through telehealth technologies.

The laws come after a June 2018 letter from the Centers for Medicare & Medicaid Services that encouraged states to utilize health technology efforts to address the opioid crisis, including through telemedicine and telepsychiatry, said Daniel Kim, an attorney with Epstein, Becker, Green and a coauthor of his firm's report.

At the same time, a number of states have expanded their controlled substance laws to allow remote prescribing through telehealth for the treatment of psychiatric or substance use disorders. Connecticut's law, for instance, allows

providers to prescribe Schedule I-III controlled substances through telehealth platforms, while banning opioid prescribing. In Indiana, 2017 legislation expanded the types of controlled medications that providers can prescribe through telehealth platforms, primarily drugs used to treat or manage opioid dependence. The states join an increasing number that have enacted laws allowing the remote prescribing of controlled substances, including Delaware, Florida, Indiana, Michigan, New Hampshire, Ohio, and West Virginia.

The new laws will enhance the availability of behavioral health services, while allowing more treatment flexibility and privacy for patients, said Ms. Dooley.

“Treatment in one's own environment where the addiction takes place is often more effective,” she said. People with addiction disorders “can also receive treatment without having to drive long distances.”

In-person requirement disappearing

As states define their telehealth policies, they are fading out a once-prevalent requirement – the in-person visit. There is no longer a single state that requires physicians to meet with patients in-person before providing telemedicine services, according to the Epstein report.

States realized that requiring in-person visits before doctors can provide telemedicine creates a barrier to care, said Mr. Kim. A move to eliminate the requirement in Texas influenced other states in phasing out the common regulation. In the widely publicized Teladoc case, the national telemedicine company sued the Texas Medical Board in 2011 over its rule requiring Texas physicians to conduct a face-to-face evaluation before treating a patient via telemedicine. The legal battle continued for years, until Teladoc voluntarily dropped its lawsuit in 2017 after Texas adopted a new law that allowed doctors to treat first-time patients through telemedicine.

Reimbursement growing, but restrictions remain

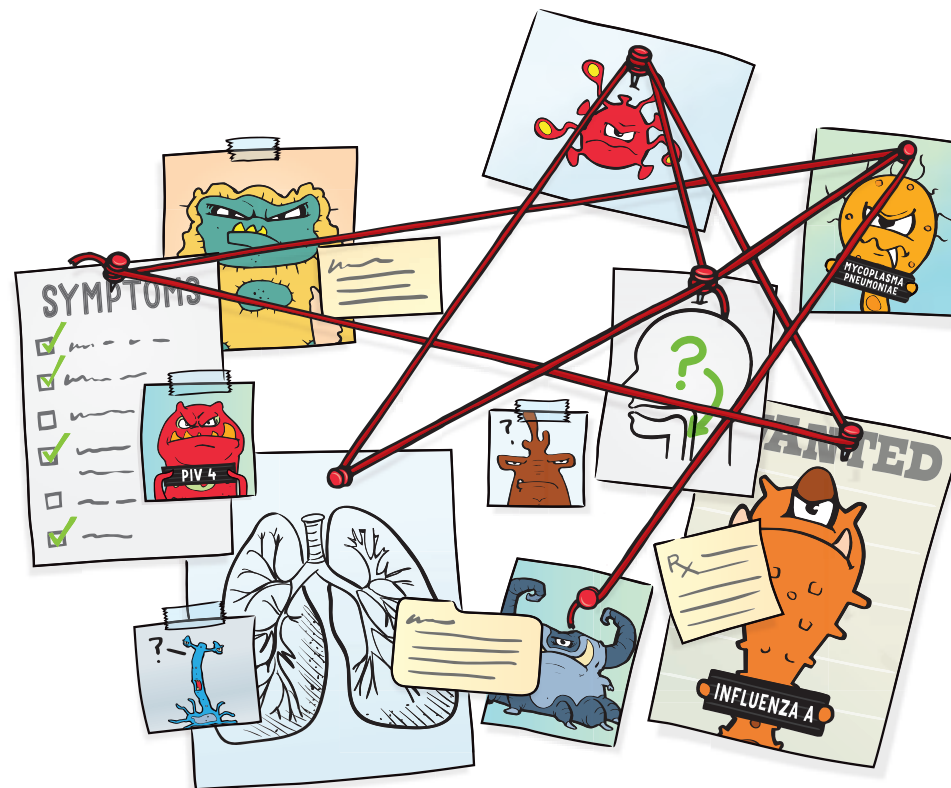
Forty-nine states and the District of Columbia reimburse for some form of telehealth, mainly live video services. At least 20 states now pay providers for remote payment monitoring (RPM), according to the Center for Connected Health Policy report. The reimbursement is often restricted, however, to certain clinical conditions and/or rules that limit the type of monitoring device allowed. Colorado, for instance, only reimburses RPM for patients with congestive heart failure, chronic obstructive pulmonary disease, asthma, or diabetes and requires that the patient was hospitalized at least twice in the last 12 months for reasons associated with one of the conditions. Missouri has similar RPM criteria associated with hospitalizations, but allows for a greater number of conditions including pregnancy, stroke, and cancer.

Most states have yet to pay for store-and-forward services, technologies that enable the electronic transfer of photos, prerecorded videos, or documents. Only about 14 states reimburse

Continued on page 16

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Exercise improves outcomes for patients with OSA

BY BIANCA NOGRADY

MDedge News

FROM THE JOURNAL CHEST®

Exercise may be as effective as CPAP in improving obstructive sleep apnea and quality of life in patients with heart failure, according to a study published in the October issue of CHEST.

Researchers undertook a randomized, four-arm trial in 65 patients with heart failure and obstructive sleep apnea, which compared the effects of CPAP alone, exercise alone – consisting of three supervised sessions per week for 3 months, or CPAP plus exercise. A control group received education sessions on the importance of exercise.

The greatest reduction in mean apnea-hypopnea index was seen in the CPAP group, who experienced

a mean decrease of 24 events per hour. The exercise plus CPAP group and the exercise only groups showed a mean decrease of 10 events per hour. In contrast, the control group showed no significant decrease in the number of events per hour of sleep.

The authors commented that the change in apnea-hypopnea index was due to reduction in obstructive apneas and hypopneas, and noted the “difficulty of accurately distinguishing obstructive from central hypopneas”.

All the active interventions were associated with significant decreases in arousal index and improvements in sleep-related saturation compared to the control intervention.

Exercise – both alone and with CPAP – was associated with an increase in maximum heart rate and peak VO_2 , and decrease in VE/VCO_2 slope compared to the CPAP-alone and control groups.

“We found that peak oxygen consumption and muscle performance improved significantly only in the exercise groups, but not with CPAP alone, even though CPAP was most effective in attenuating OSA severity,” wrote Denise M. Servantes, MD, from the Departamento de Psicobiologia at the Universidade Federal de São Paul in Brazil, and co-authors. “Because peak VO_2 is an independent predictor

of survival and crucial to the optimal timing of cardiac transplantation, these findings have important clinical implications, even in patients who are adherent to CPAP.”

A significant number of participants in the active intervention groups changed New York Heart Association functional class; the number of patients in the exercise group in class I went from 0% to 88% by 3 months, in the CPAP group it increased from 0% to 47%, and in the CPAP plus exercise group, it increased from 0% to 73%.

The study also found evidence of a trend toward improved sexual function in the participants who undertook both exercise plus CPAP.

All patients in the intervention groups showed improvements in subjective daytime sleepiness and quality of life, although improvements in the Minnesota Living With Heart Failure Questionnaire and Short Form Health Survey (SF-36) were significant only in the two groups that did exercise.

“The data suggest that exercise could be a therapeutic option for patients with HF and OSA who refuse CPAP or are intolerant to it,” the authors wrote. “In this regard, a considerable number of patients with HF and OSA do not experience subjective excessive daytime sleep-

iness and consequently observe no immediate benefit from using CPAP, which could contribute to poor long-term adherence.”

Individuals in the exercise group showed a slight but significant weight reduction, and those who undertook the exercise program also showed significant improvements in muscle strength and endurance compared to the control group.

The authors commented that another study examining the impact of weight loss program in people with moderate to severe obstructive sleep apnea found weight loss only or combined interventions achieved benefits for C-reactive protein levels, insulin resistance, and serum triglyceride levels. But these benefits weren't seen with CPAP alone.

“The results of that study, and the present one emphasize the importance of adjunctive therapy of OSA with weight loss and exercise when applicable.”

They did acknowledge that the short duration of the study, and small sample size were limitations, and that this was a preliminary investigation.

No conflicts of interest were declared.

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SOURCE: Servantes D et al. CHEST. 2018;154:808-817.



DIGITAL VISION/THINKSTOCK

Continued from page 14

for such technology, and many policies include limitations. California, for example, only reimburses for store-and-forward services in teledermatology, teledentistry, and teleophthalmology. Connecticut allows for store-and-forward payment between physicians through email. Missouri allows for store-and-forward services in orthopedics, dermatology, optometry, ophthalmology, and in cases of retinopathy, burn and wound care, dental services, and maternal-fetal ultrasounds.

Reimbursement for telehealth is still a challenge for many physicians, Dr. Sumner said. Part of the problem is the wide discrepancy in how telehealth is defined among states, she said. Some states only consider live or interactive two-way technology as telehealth, excluding services such as store-and-forward and RPM. Other states reimburse for certain technology-based services, but they do not consider them telehealth. Maryland's Medicaid

program for example, does not reimburse for store and forward under its telehealth policy. However, store and forward used in dermatology, radiology, and ophthalmology is reimbursed by Maryland under an alternative billing code, though not considered telehealth.

Establishing best practices in telehealth through careful evaluation and research would improve reimbursement, said S. David McSwain, MD, interim chief medical information officer at the Medical University of South Carolina, Charleston, and medical director for telehealth optimization.

“We can use that evidence to reduce the variation in telehealth payment policies across the states,” Dr. McSwain said in an interview. “By leveraging reimbursement models to promote best practices, we can encourage the spread of telehealth services that have the greatest impacts on patients, their families, and the health care system.”

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FDA approves Xyrem to treat children with narcolepsy

BY RICHARD PIZZI

MDedge News

The Food and Drug Administration has cleared Xyrem (sodium oxybate) oral solution to treat cataplexy and excessive daytime sleepiness in patients ages 7-17 with narcolepsy.

The central nervous system depressant previously had been approved to treat cataplexy in adults with narcolepsy.

The current approval was granted by the FDA under a Priority Review designation. Xyrem also received the FDA's Orphan Drug designation, which is intended to encourage the development of drugs for rare diseases.

The agency noted in a press release, however, that the drug would continue to be available

only through risk evaluation mitigation strategy (REMS) programs because of “the risk of serious outcomes resulting from inappropriate prescribing, misuse, abuse and diversion.”

Xyrem either alone or in combination with other CNS depressants may be associated with reactions including seizure, respiratory depression, decreases in the level of consciousness, coma, and death, the

FDA said.

The most common adverse reactions in pediatric patients were enuresis, nausea, headache, vomiting, weight decrease, decreased appetite, and dizziness.

For more information on prescribing Xyrem for pediatric patients, see the revised labeling information on the FDA website.

rpizzi@mdedge.com



Apixaban's comparative efficacy assessed by AHRQ

BY ANDREW D. BOWSER

MDedge News

Among direct oral anticoagulants, apixaban (Eliquis) has shown fewer stroke events and bleeding than warfarin in patients with atrial fibrillation, according to results of an updated comparative effectiveness review.

Dabigatran (Pradaxa), by contrast, has shown reductions in stroke events but a similar rate of bleeding events compared to warfarin, according to the report from the Duke Evidence-based Practice Center, Durham, N.C.

Rivaroxaban (Xarelto), meanwhile, is "similar in both benefits and harms with warfarin" in evidence to date, investigators wrote in the report, which was prepared for the Agency for Healthcare Research and Quality (AHRQ) and the Patient-Centered Outcomes Research Institute (PCORI).

Finally, edoxaban (Savaysa) is "most likely similar" to warfarin with respect to preventing stroke or systemic embolism, with less risk for major bleeding and hemorrhagic stroke, investigators wrote in a summary of their findings on the AHRQ website.

"Effectiveness of these direct oral anticoagulants as compared to one another however is limited by the lack of randomized studies directly comparing their safety and effectiveness," concluded investigators, led by Gillian D. Sanders, PhD, of Duke University.

The 612-page report details a systematic review based on 320 articles representing 185 unique studies. The review was designed to update a 2013 AHRQ report that evaluated evidence not only for treatment options to prevent stroke in patients with atrial fibrillation, but also for tools used to predict risk of stroke or bleeding.

In the 2013 report, investigators concluded that the newer anticoagulants showed "early promise" in reducing stroke and bleeding events compared with warfarin.

That earlier report said that CHA₂ and CHA₂DS₂-VASc had the best evidence to support prediction of stroke events, while HAS-BLED provided the best discrimination of bleeding risk.

The updated report adds the ABC stroke risk score as a tool that, along with CHADS₂ and CHA₂DS₂-VASc, has the "best evidence" predicting thromboembolic risk, authors said.

Imaging tools, on the other hand, still need more evidence supporting their use to predict thromboembolic risk, Dr. Sanders and colleagues said in their report.

The literature review, which

covered the January 2000 through February 2018, turned up 61 studies relevant to predicting thromboembolic risk, 38 on bleeding risk, and 117 on preventing thromboembolic events with anticoagulation therapies,

antiplatelet therapies, or procedures. chestphysiciannews@chestnet.org

SOURCE: Sanders GD et al. 2018 Oct 30. AHRQ Publication No. 18(19)-EHC018-EF.

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Lower glucose targets for cardiac patients revisited

BY BIANCA NOGRADY

MDedge News

FROM THE JOURNAL CHEST®

Tighter glucose control while minimizing the risk of severe hypoglycemia is associated with lower mortality among critically ill cardiac patients, new research suggests.

Researchers reported in CHEST on the outcomes of a multicenter retrospective cohort study in 1,809

than .001). The lower mortality in the lower target group was evident among both diabetic (4.7% vs. 12.9%; P less than .001) and nondiabetic patients (4.1% vs. 7.4%; $P = .02$).

Researchers also saw that unadjusted 30-day mortality increased with increasing median glucose levels; 5.5% in patients with a blood glucose of 70-110 mg/dL, 8.3% mortality in those with blood glucose

“Our results further the discussion about the appropriate BG [blood glucose] target in the critically ill because they suggest that the BG target and severe hypoglycemia effects can be separated.”

adults in cardiac ICUs. Patients were treated either to a blood glucose target of 80-110 mg/dL or 90-140 mg/dL, based on the clinician's preference, but using a computerized ICU insulin infusion protocol that the authors said had resulted in low rates of severe hypoglycemia.

The study found patients treated to the 80-110 mg/dL blood glucose target had a significantly lower unadjusted 30-day mortality compared to patients treated to the 90-140 mg/dL target (4.3% vs. 9.2%; P less

than .001). The lower mortality in the lower target group was evident among both diabetic (4.7% vs. 12.9%; P less than .001) and nondiabetic patients (4.1% vs. 7.4%; $P = .02$).

Patients treated to the 80-110 mg/dL blood glucose target were more likely to experience an episode of moderate hypoglycemia, compared with those in the higher target group (18.6% vs. 8.3%; P less than .001). However, the rates of severe hypoglycemia were low in both groups, and the difference between the low and high target groups did not reach statistical significance

VIEW ON THE NEWS

Rethink blood glucose targets for critically ill patients?

After the multicenter NICE-SUGAR trial showed higher 90-day mortality in patients treated with intensive insulin therapy to lower blood glucose targets, compared with more moderate targets, enthusiasm has waned for tighter blood glucose control, James S. Krinsley, MD, argued in an editorial accompanying the study (CHEST. 2018;154[5]:1004-5). But the assumption of a “one-size-fits-all” approach to glucose control in the critically ill is a potential flaw of randomized clinical trials, he noted, and some patients may be better suited to tighter control than others. This study has shown that standardized protocols, including frequent measurement of blood glucose, can safely achieve tight blood glucose control in the ICU with low rates of hypoglycemia. If these findings are confirmed in larger multicenter clinical trials, it should prompt a rethink of blood glucose targets in the critically ill, he concluded.

Dr. Krinsley is director of critical care at Stamford (Conn.) Hospital and clinical professor of medicine at the Columbia University College of Physicians and Surgeons, New York. He declared consultancies or advisory board positions with Edwards Life Sciences, Medtronic, OptiScan Biomedical, and Roche Diagnostics.

(1.16% vs. 0.35%; $P = .051$).

The authors did note that patients whose blood glucose dropped below 60 mg/dL showed increased mortality, regardless of what target they was set for them. The 30-day unadjusted mortality in these patients was 15%, compared with 5.2% for patients in either group who did not experience a blood glucose level below 60 mg/dL.

“Our results further the discussion about the appropriate BG [blood glucose] target in the critically ill because they suggest that the BG target and severe hypoglycemia effects can be separated,” wrote Andrew M. Hersh, MD, of the division of pulmonary and critical care at San Antonio Military Medical Center, and his coauthors.

But they said the large differences in mortality seen between the two treatment targets should be interpreted with caution, as it was difficult to attribute that difference solely to an 18 mg/dL difference in blood glucose treatment targets.

“While we attempted to capture factors that influenced clinician choice, and while our model successfully achieved balance, suggesting that residual confounding was minimized, we suspect that some of the mortality signal may be attributable to residual confounding,” they wrote.

Another explanation could be that hypoglycemia was an ‘epiphenomenon’ of multiorgan failure, as some studies have found that both sponta-

neous and iatrogenic hypoglycemia were independently associated with mortality. “However, given the very-low rates of severe hypoglycemia found in both groups it is unlikely that this was a main driver of the mortality difference found,” the investigators wrote.

The majority of patients in the study had been admitted to the hospital for chest pain or acute coronary syndrome (43.3%), while 31.9% were admitted for cardiothoracic surgery, 6.8% for heart failure including cardiogenic shock, and 6% for vascular surgery.

The authors commented that a safe and reliable protocol for intensive insulin therapy, with high clinician compliance, could be the key to realizing its benefits, and could be aided by recent advances such as closed-loop insulin delivery systems.

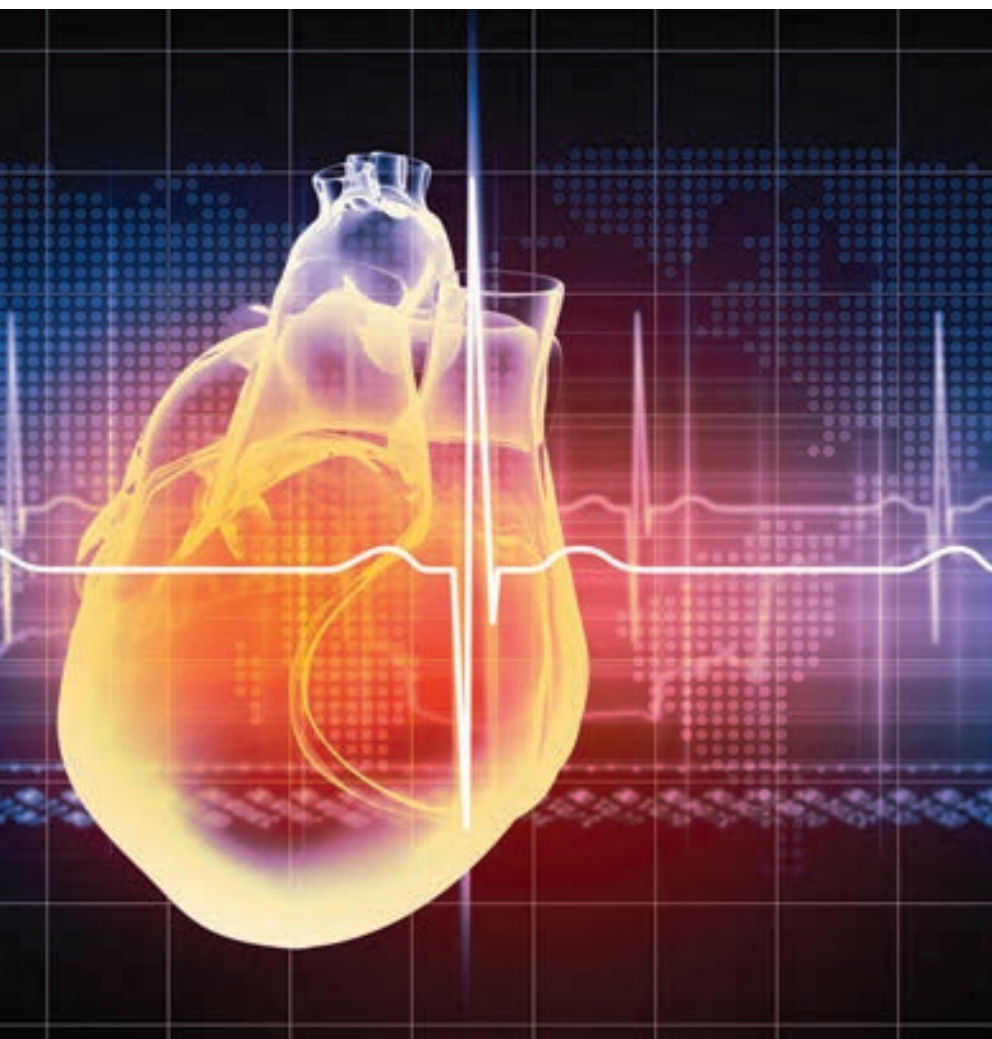
They also stressed that their results did not support a rejection of current guidelines and instead called for large randomized, clinical trials to find a balance between benefits and harms of intensive insulin therapy.

“Instead our analysis suggests that trials such as NICE-SUGAR, and the conclusion they drew, may have been accurate only in the setting of technologies, which led to high rates of severe hypoglycemia.”

No conflicts of interest were declared.

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SOURCE: Hersh AM et al. CHEST. 2018 Nov;154(5):1044-51.



THINKSTOCK

Endothelin receptor antagonist effective for PoPH

BY TED BOSWORTH

MDedge News

PARIS – In a multicenter, placebo-controlled trial conducted in patients with portopulmonary hypertension (PoPH), macitentan, an endothelin receptor antagonist, achieved significant improvements in a number of hemodynamic measures, including the primary endpoint of pulmonary vascular resistance, according to a late-breaking presentation at the annual congress of the European Respiratory Society.

“This is the first randomized, controlled trial that enrolled only patients with PoPH, and it demonstrates that a therapy used in pulmonary arterial hypertension improves hemodynamics in PoPH,” reported Olivier Sitbon, MD, of the Centre des Maladies Vasculaires Pulmonaires, Université de Paris–Sud, Clamart, France.

PoPH, defined by accompanying portal hypertension, is a variant on pulmonary arterial hypertension (PAH). Liver dysfunction is common but not required for a diagnosis.

Although patients often receive therapies known to be effective in PAH, such as drugs in the endothelin receptor antagonist class, prostanoids, or phosphodiesterase-5 inhibitors, there “are very limited data” demonstrating efficacy of any drug specifically for patients with PoPH, according to Dr. Sitbon. One reason is that PoPH has been an exclusion criterion in large PAH treatment trials.

In PORTICO, a double-blind trial presented by Dr. Sitbon, 85 PoPH patients were random-

ized to 10 mg macitentan or placebo. Essentially, all were in World Health Organization functional class II or III with a median 6-minute walk distance (6MWD) of about 385 meters. During the trial, patients were permitted to remain on baseline therapies, including prostanoids and phosphodiesterase-5 inhibitors when doses had been stable for at least 3 months prior to randomization.

The primary endpoint was change in pulmonary vascular resistance (PVR) at 12 weeks.

Although patients often receive therapies known to be effective in PAH, such as drugs in the endothelin receptor antagonist class, prostanoids, or phosphodiesterase-5 inhibitors, there “are very limited data” demonstrating efficacy of any drug specifically for patients with PoPH.

Other hemodynamic changes, such as change in cardiac index and total pulmonary resistance, were included in secondary endpoints along with change in WHO class and change in 6MWD.

When compared at 12 weeks with a model-adjusted ratio of geometric means, the ratio of PVR for the treatment to experimental arms was 0.65, which was a 35% relative improvement (P less than .0001) with macitentan.

The relative reduction from baseline in total arterial pressure was also highly significant favoring

macitentan (-199.8 vs. -18.3 dyne/sec per cm^{-5} ; P less than .0001). Mean pulmonary pressure was slightly increased at the end of 12 weeks relative to baseline in the placebo group ($+0.4$ mm Hg) but fell 6.4 mm Hg in the treatment group (P less than .0001). In addition, cardiac index improved substantially on macitentan but not on placebo (0.6 vs. 0.1 L/min per m^2 ; $P = .0009$).

However, there were no significant differences at the end of 12 weeks between groups for change from baseline in WHO functional class or 6MWD. Change in hepatic venous pressure gradient was evaluated in patients with liver disease, but macitentan was not associated with any effect on this parameter.

Macitentan was well tolerated overall. Although one patient experienced a equal to or greater than three times the upper limit of normal elevation of liver enzymes, Dr. Sitbon reported that there were no other hepatic safety concerns. Overall, he characterized the safety of macitentan in PoPH as “consistent with that previously observed in PAH.”

Larger and longer-term trials are needed to evaluate the impact of treatment on clinical events, but Dr. Sitbon indicated that these results demonstrate acceptable safety and tolerability and a favorable effect on hemodynamics. He further suggested that this randomized study provides a first step toward establishing an evidence-based treatment in this disease.

Dr. Sitbon reported financial relationships with Bayer, GlaxoSmithKline, and Actelion, the sponsor of this trial.

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Short-term NSAIDs appear safe for high-risk patients

BY WILL PASS

MDedge News

Short-term prescription NSAIDs appeared safe in high-risk patients with musculoskeletal disease and chronic kidney disease (CKD), hypertension, or heart failure, in a retrospective, observational study.

The findings of the study challenge the Choosing Wisely cam-

“While these recommendations offer basic analgesics and nonpharmacological treatments as preferable alternatives, it is both possible and disconcerting that some physicians might instead prescribe opioids, which typically pose elevated risk of adverse events and dependence vs. NSAIDs,” the investigators wrote. The report is in JAMA Internal Medicine.

The investigators found that prescribing rates varied widely, ranging from 6.7% to 14.4% of different health regions, and from 0.9% to 60.3% among 688 primary care practices, with “substantial variation in use” among primary care physicians.

paign of the American Society of Nephrology, which recommends against NSAIDs for high-risk patients, according to lead author Zachary Bouck, MPH, of the department of medicine at Sunnybrook Health Sciences Centre in Toronto, and his coauthors.

They sought to estimate the frequency and characteristics of NSAID prescriptions while also looking for associations with acute renal and cardiovascular complications. The retrospective, observational study involved 814,049 adults with musculoskeletal disease and

7,365 primary care physicians in Ontario, Canada. All patients were aged 65 years and older, and had been diagnosed with hypertension, chronic kidney disease, or heart failure in the past year. Instances in which a patient was prescribed an NSAID within 7 days of presentation were included.

To assess for associations between prescription NSAIDs and negative outcomes, the investigators searched for renal or cardiovascular complications within 37 days of presentation. Over-the-counter NSAID usage was not evaluated.

There were 224,825 visits. An NSAID was prescribed after 9.3% of these visits.

Renal and cardiovascular outcomes were similar between high-risk patients who received a prescription NSAID and those who did not (absolute risk reduction, .0003; $P = .74$).

“The similarity in risk between users and nonusers, each group primarily consisting of patients



DENISE FULTON/MDEDGE NEWS

with hypertension, suggests that the short-term association of NSAIDs in high-risk patients with musculoskeletal pain may not be as dangerous as initially thought,” the authors concluded.

The investigators found that prescribing rates varied widely, ranging from 6.7% to 14.4% of different health regions, and from 0.9% to

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VIEW ON THE NEWS

Observational studies require skepticism

The study by Bouck and colleagues found that short-term prescription NSAIDs were safe for high-risk patients; however, physicians should consider the inherent limitations of observational studies before altering clinical decisions, according to Jonathan Zipursky, MD, and David N. Juurlink, MD, PhD. This is particularly important since the findings challenge the American Society of Nephrology, which recommends against NSAIDs in patients with chronic kidney disease, heart failure, or hypertension.

Among the advantages of observational studies over randomized trials is that they often include patients not eligible for randomized controlled trials, “and extended follow-up enables examination of outcomes that might not have arisen earlier in treatment,” they wrote in an editorial. “Moreover, sample sizes often greatly exceed those of RCTs, facilitating detection of less common adverse events. Consequently, population-based observational studies are critical to post-marketing surveillance.”

On the other hand, observational studies are less tightly controlled than randomized trials, with nonrandomized allocation, which “raises the possibilities of selection bias and confounding by indication,” they wrote. Furthermore, “readers are left questioning whether patients who were not prescribed NSAIDs were simply taking over-the-counter medications (including NSAIDs),” they wrote.

“Although we rely on observational studies to answer questions poorly suited to clinical trials, we have to interpret these findings with caution,” they added.

Dr. Zipursky and Dr. Juurlink are with the department of medicine at Sunnybrook Health Sciences Centre in Toronto. These comments are adapted from their accompanying editorial (JAMA Intern Med. 2018 Oct 8. doi: 10.1136/ebmed-2016-110401).

Continued from previous page

60.3% among 688 primary care practices, with “substantial variation in use” among primary care physicians.

The authors acknowledged limitations, including the use of administrative data, but noted that their study, showing substantial variations in NSAID prescribing, “along with

the identification of patient and physician characteristics associated with NSAID use, presents an opportunity for quality improvement, with some potential targets for any resulting interventions,” they wrote.

The Institute for Clinical Evaluative Sciences funded the study. The authors reported compensation from the Canadian Institute of

Health Research, the department of family and community medicine at the University of Toronto, the Heart and Stroke Foundation of Canada, and Women’s College Hospital.

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SOURCE: Bouck Z et al. JAMA Intern Med. 2018 Oct 8. doi: 10.1001/jamainternmed.2018.4273.

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DECLARE: Dapagliflozin linked to better CV outcomes

BY WILL PASS

MDedge News

For patients with type 2 diabetes who have or are at risk for atherosclerotic cardiovascular

disease, dapagliflozin is associated with a lower composite rate of cardiovascular death or hospitalization for heart failure, compared with placebo, according to investigators.

A composite measure of major ad-

verse cardiovascular events, including cardiovascular death, ischemic stroke, or myocardial infarction, was comparable between dapagliflozin and placebo; in contrast, diabetic ketoacidosis occurred more fre-

quently with dapagliflozin, reported lead author Stephen D. Wiviott, MD at the American Heart Association scientific sessions.

“As a result of [the] intersection of

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diabetes, atherosclerotic cardiovascular disease, and heart failure, the importance of determining diabetes therapies that are not only safe but also effective in reducing cardiovascular risk is paramount," Dr. Wiviott and colleagues wrote in an article published simultaneously in the *New England Journal of Medicine*.

"Dapagliflozin is a selective inhibitor of sodium–glucose cotransporter (SGLT2) that blocks glucose resorption in the proximal tubule of the kidney and promotes glucosuria," the investigators wrote. "Other SGLT2 inhibitors have shown favorable cardiovascular effects, including a reduction in the risk of hospitalization for heart failure, predominantly in

patients with type 2 diabetes and established cardiovascular disease; they have also been shown to delay the progression of kidney disease."

The goal of the Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE–TIMI 58) trial was to determine what impact, if any, dapagliflozin has on renal and cardiovascular

outcomes in a diverse array of patients with or at risk for atherosclerotic cardiovascular disease. The phase 3, double-blind, placebo-controlled, randomized study involved 17,160 adults with type 2 diabetes from 33 countries. Of these, nearly 7,000 patients had atherosclerotic cardiovascular disease and the remaining 10,000 or so patients had multiple risk factors for

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atherosclerotic cardiovascular disease. Patients were at least 40 years of age, had a creatinine clearance of at least 60 mL/minute, and a hemoglobin A_{1c} level between 6.5% and 12.0%. They were randomly assigned to receive either dapagliflozin 10 mg daily or placebo. Every 6 months, patients had laboratory testing with in-person follow-up for safety, clinical response,

and adherence; patients were contacted via telephone at the halfway point between appointments (3 months).

The primary safety outcome of the study was major adverse cardiovascular outcomes (ischemic stroke, myocardial infarction, or cardiovascular death). The trial began with MACE as the sole pri-

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Dr. Stephen D. Wiviott and his co-investigators noted that determining diabetes therapies that are not only safe but also effective in reducing cardiovascular risk is paramount.

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Continued from previous page

primary safety outcome, as guided by the Food and Drug Administration, but this changed before completion. “During the trial,” the investigators explained, “compelling external scientific information from the EMPA-REG OUTCOME trial, which evaluated another SGLT2 inhibitor, showed greater benefit with respect

to cardiovascular death and hospitalization for heart failure than with respect to MACE.” Therefore, before data were known, the investigators added a second primary outcome: a composite of cardiovascular death or hospitalization for heart failure. The two secondary outcomes were a renal composite (new end-stage renal disease, estimated glomerular

filtration rate decrease by at least 40% to less than 60 mL/min per 1.73 m² of body-surface area, or death from renal or cardiovascular disease), and death from any cause.

The primary safety outcome (MACE rate) showed that dapagliflozin was noninferior to placebo (upper boundary of the 95% confidence interval, less than 1.3; *P* less

than .001 for noninferiority). Although the MACE rate was similar between treatment groups (8.8% for dapagliflozin vs. 9.4% for placebo; *P* = .017), the composite rate of cardiovascular death or hospitalization for heart failure was 17% lower for patients receiving dapagliflozin, compared with those who received placebo (4.9% vs. 5.8%); this latter finding was attributable mostly to a 27% lower risk of hospitalization, instead of the 2% reduction in cardiovascular death. Seven percent fewer deaths of any kind were observed in the dapagliflozin group (6.2%) than in the placebo group (6.6%). Renal events saw a bigger

“In a broad population of patients with type 2 diabetes [dapagliflozin] did result in a significantly lower rate of cardiovascular death or hospitalization for heart failure than placebo.”

difference, of 23% (4.3% vs. 5.6%).

Statistically significant adverse events seen in more dapagliflozin than placebo patients included diabetic ketoacidosis and genital infection. Dr. Wiviott noted that adverse events favoring hypoglycemia included major hypoglycemia and bladder cancer.

“We did not find that SGLT2 inhibition with dapagliflozin resulted in a lower rate of cardiovascular death or death from any cause than placebo, a finding that contrasts with that in the EMPA-REG OUTCOME trial,” the investigators noted. Apart from possible differences in drugs within the same class, the investigators pointed to more restrictive renal criteria in the DECLARE trial and possible inherent differences between patient populations, among other possible factors.

“In a broad population of patients with type 2 diabetes [dapagliflozin] did result in a significantly lower rate of cardiovascular death or hospitalization for heart failure than placebo, with additional findings supporting a possible lower rate of adverse renal outcomes,” the investigators concluded.

The DECLARE-TIMI 58 trial was sponsored by AstraZeneca and Bristol-Myers Squibb. Authors reported various financial affiliations with Eisai, Medtronic, Sanofi Aventis, Abbott, Regeneron, and others.

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SOURCE: Wiviott SD et al. *N Engl J Med.* 2018 Nov 10. doi: 10.1056/NEJMoa1812389.

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Shared decision making for pacemaker implantation

BY ANDREW D. BOWSER

MDedge News

A new clinical practice guideline on the management of bradycardia and cardiac conduction system disorders in adults emphasizes the importance of patient-centered care and “shared decision-making” between patient and clinician, particularly with regard to patients who have indications for pacemaker implantation.

Shared decision making extends to the end-of-life setting where “complex” informed consent and refusal of care decisions need to be patient specific, and must involve all stakeholders, according to the new 2018 guidelines from the American College of Cardiology (ACC), American Heart Association (AHA), and Heart Rhythm Society (HRS).

“Patients with decision-making capacity or his/her legally defined surrogate has the right to refuse or request withdrawal of pacemaker therapy, even if the patient is pacemaker dependent, which should be considered palliative, end-of-life care, and not physician-assisted suicide,” the guidelines read.

The guidelines additionally update the evaluation and treatment of sinus node dysfunction, atrioventricular block, and conduction disorders, based in part on a comprehensive evidence review conducted from January to September 2017. They

supersede a 2008 guideline from the three societies on device-based therapy of cardiac rhythm abnormalities, and the focused update to that guideline published in 2012.

These guidelines will be useful not only to arrhythmia specialists, but also to internists and family physicians, cardiologists, surgeons, emergency physicians, and anesthesiologists, according to the guideline writing committee, which included representatives of ACC, AHA, HRS, and several other national organizations. The committee included cardiac electrophysiologists, cardiologists, surgeons, an anesthesiologist, and other clinicians, as well as a patient/lay representative, and was chaired by Fred M. Kusumoto, MD, of Mayo Clinic Florida.

For sinus node dysfunction, no minimum heart rate or pause duration has been determined for which permanent pacing would be recommended, the guidelines state. To determine whether permanent pacing is necessary in those patients, clinicians should work to establish a temporal correlation between bradycardia and symptoms, according to

“Patients with decision-making capacity or his/her legally defined surrogate has the right to refuse or request withdrawal of pacemaker therapy, even if the patient is pacemaker dependent.”

the guideline authors.

Left bundle branch block, when found on echocardiogram, greatly increases the chances of underlying structural heart disease and of a left ventricular systolic dysfunction diagnosis, according to the guidelines, which state that echocardiography is the most appropriate initial screening test for left ventricular systolic

dysfunction and other structural heart disease.

Permanent pacing is recommended for certain types of atrioventricular (AV) block, according to the guidelines, which include high-grade AV block, acquired second-degree Mobitz type II AV block, and third-degree AV block not related to reversible or physiologic causes.

Treatment of sleep apnea can reduce frequency of nocturnal bradycardia and may provide a cardiovascular benefit, the guideline authors state. Patients with nocturnal bradycardias should be screened for sleep apnea, though authors cautioned that these arrhythmias are not, in and of themselves, an indication for permanent pacing.

“Treatment decisions are based not only on the best available evidence, but also on the patient’s goals of care and preferences,” Dr. Kusumoto said in a press release jointly issued by the ACC, AHA, and HRS. Emerging pacing technologies such as His-bundle pacing and transcatheter leadless pacing systems need more study to determine which patient populations will benefit most from them, the guidelines state.

“Regardless of technology, for the foreseeable future, pacing therapy requires implantation of a medical device,” Dr. Kusumoto said. “Future studies are warranted to focus on the long-term implications associated with lifelong therapy.”

The 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients With Bradycardia and Cardiac Conduction Delay is now published in the Journal of the American College of Cardiology, and simultaneously in the journals Circulation and HeartRhythm.

Dr. Kusumoto reported no relationships with industry or other entities. Guideline co-authors provided disclosures related to Boston Scientific, Janssen Pharmaceuticals, Medtronic, Daiichi-Sankyo, Sanofi-Aventis, St. Jude Medical, and Abbott, among others.

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SOURCE: Kusumoto FM et al. J Am Coll Cardiol. 2018 Nov 6.

Is prehospital cooling in cardiac arrest ready for prime time?

BY RICHARD MARK KIRKNER

MDedge News

CHICAGO – Starting transnasal evaporative cooling before patients in cardiac arrest arrive at the hospital has been found to be safe, according to study results presented at the American Heart Association scientific sessions.

The European trial didn’t determine any benefit in the out-of-hospital approach, compared with in-hospital cooling across all study patients. But it did suggest that patients with ventricular fibrillation may achieve higher rates of complete neurologic recovery with the prehospital cooling approach.

“Transnasal evaporative cooling in out-of-hospital cardiac arrest is hemodynamically safe,” said Per Nordberg, MD, PhD, of Karolinska Institute in Stockholm, reporting for the Prehospital Resuscitation Intra-Arrest Cooling Effectiveness Survival Study (PRINCESS). “I think this an important message, because guidelines state at the moment that you shouldn’t cool patients outside the hospital. We have shown that

this is possible with this new method.”

Transnasal evaporative cooling (RhinoChill) is a noninvasive method that involves cooling of the brain and provides continuous cooling without volume loading.

Centers in seven European countries participated in the trial, randomizing 677 patients to the transnasal, early cooling protocol or standard in-hospital hypothermia. The final analysis evaluated 671 patients: 337 in the intervention group and 334 in the control group. In the intervention group, the transnasal cooling technique was started on patients during CPR in their homes or in the ambulance.

The study found that the rate of 90-day survival with good neurological outcome was 16.6% in the intervention group, compared with 13.5% in the control group, a nonsignificant difference ($P = .26$).

“However, we could see a signal or a clinical trend toward an improved neurologic outcome in patients with ventricular fibrillation,” Dr. Nordberg said: 34.8% vs. 25.9% for the intervention vs. control populations, a relative, nonsignificant

difference of 25% ($P = .11$).

In terms of complete neurologic recovery, the differences between the treatment groups among those with ventricular fibrillation were even more profound, and significant: 32.6% vs. 20% ($P = .002$).

In his discussion of the trial, Christopher B. Granger, MD, of Duke University, Durham, N.C., noted that the trial was well conducted and that it confirmed that patients can be rapidly cooled during or immediately after cardiac arrest. “But we still do not know if this has meaningful improvement in clinical outcomes,” he cautioned. A strength of the trial is its size, particularly “in a very challenging setting,” Dr. Granger added.

He reported receiving funding from the Swedish Heart-Lung Foundation. The makers of RhinoChill provided the cooling device used in the study at no cost to the participating sites.

Dr. Granger reported numerous financial relationships.

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SOURCE: Nordberg P et al. AHA Scientific Sessions-Abstract 2018-LBCT-18598-AHA.

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Home telemonitoring for heart failure cuts mortality

BY BRUCE JANCIN

MDedge News

MUNICH – A comprehensive home telemonitoring program paid off big for selected patients with heart failure in a large, German nationwide masked randomization trial.

In the 1,538-patient Telemedical Interventional Management in Heart Failure II (TIM-HF2) trial, participants randomized to the non-invasive home monitoring program had a 30% reduction in all-cause mortality during 12-13 months of

information was immediately analyzed using proprietary telemedical analytic software known as the Fontane system. The software employs individually tailored, self-adapting algorithms in order to alert staff when trouble is brewing.

But the telemonitoring intervention doesn't merely detect early clinical deterioration. It's also a vehicle for ongoing patient education, outpatient adjustment of drugs, management of major comorbid conditions, and hospital admissions as needed. The patient's local primary

care physician was also plugged into the remote monitoring system and kept abreast of the patient's condition. Second, TIM-HF2 focused on a carefully selected subgroup of heart failure patients whom prior studies suggested were particularly likely to benefit from home telemedical management. All participants were NYHA class II or III with a left ventricular ejection fraction of 45% or less, a hospitalization for heart failure within 12 months prior to randomization, and free of moderate or severe depression as evidenced by a baseline Patient Health Questionnaire-9 score of 9 or less, explained Dr. Koehler, head of the center for cardiovascular telemedicine at Charite University in Berlin.

Why exclude patients with depression? “In this concept, with wholistic remote patient management, we need an active patient who is able to measure every day, who is able to communicate with the telemedical center, and who is able to communicate in this network created between the telemedical center and local caregivers. If someone is really depressed, unable to act, lying in bed saying it makes no sense to take drugs or do anything, then we cannot help. That is for us, I think, the most important thing. We've seen it now in two trials,” according to the cardiologist.

The all-cause mortality rate was 7.86 per 100 person-years in the home-telemonitoring group versus 11.34 in usual-care controls. Patients in the active intervention arm lost a mean of 17.8 days per year because of unplanned cardiovascular hospital admissions, compared with 24.2 days per year in controls.

Importantly, outcomes were equally good in the remote patient-management group regardless of whether patients were among the 40% of participants living in urban Germany or the 60% in rural areas. Thus, the telemonitoring intervention eliminated the geographic disparity in health care outcomes which is a prominent issue in Germany, as well as the United States.

A formal cost-benefit analysis of the TIM-HF2 results is in the works, Dr. Koehler said.

Simultaneous with his presentation in Munich, the TIM-HF2 study was published online in the Lancet.

In an accompanying editorial, two prominent heart failure experts – John F.G. Cleland, MD, of the University of Glasgow, and Robin A. Clark, MD, of Flinders University in Adelaide – hailed TIM-HF2 as a major advance and indicated in sharp terms that it's time for guideline writers to sit up and take notice.

“Despite much clinical skepticism and feeble support from most guidelines, in our view the growing weight of evidence suggests that home telemonitoring does reduce mortality for patients with heart failure, and this effect might be substantial. These and other trials also show that the emphasis placed on hospital admission for heart failure might be misplaced, at least from a patient's perspective, because the proportion of days lost due to hospital admission is small, compared with those lost to death,” the physicians wrote in the editorial.

They also noted that, even though

the between-group difference in the number of days during which patients were hospitalized for cardiovascular causes was relatively small, it's clear that home telemonitoring triggered some potentially life-saving hospitalizations. “Home

Outcomes were equally good in the remote patient-management group regardless of whether patients were among the 40% of participants living in urban Germany or the 60% in rural areas.

telemonitoring puts the patient back in the center of health care, ensuring that they know what the health professional is trying to achieve and that they agree with those aims. Ultimately, patients and their families are a large and relatively untapped health care resource,” they wrote.

The TIM-HF2 trial was funded by the German Federal Ministry of Education and Research. Dr. Koehler reported receiving speaking and/or consultant fees from Novartis, Abbott, and Medtronic.

bjancin@mdedge.com

SOURCE: Koehler F et al. ESC Congress 2018. Lancet. 2018 Sep 22;392(10152):1047-57.



BRUCE JANCIN/MDEDGE NEWS

Dr. Friedrich Koehler said, “In this concept, with wholistic remote patient management, we need an active patient who is able to measure every day, who is able to communicate with the telemedical center.”

prospective follow-up, compared with control subjects randomized to guideline-directed usual care. They also experienced an average of 6 fewer days of unplanned cardiovascular hospitalizations, Friedrich Koehler, MD, reported at the annual congress of the European Society of Cardiology.


Previous studies of home telemonitoring in heart failure patients have yielded mixed results. Dr. Koehler cited two explanations why TIM-HF2 was unreservedly positive while some other studies failed to demonstrate significant benefit.

First, TIM-HF2 didn't rely on passive monitoring of the patients' daily electronically submitted home data. Instead, the data went straight to a central telemonitoring center staffed 24/7 by physicians and nurses with heart failure expertise. There, the

ry care physician was also plugged into the remote monitoring system and kept abreast of the patient's condition.


Second, TIM-HF2 focused on a carefully selected subgroup of heart failure patients whom prior studies suggested were particularly likely to benefit from home telemedical management. All participants were NYHA class II or III with a left ventricular ejection fraction of 45% or less, a hospitalization for heart failure within 12 months prior to randomization, and free of moderate or severe depression as evidenced by a baseline Patient Health Questionnaire-9 score of 9 or less, explained Dr. Koehler, head of the center for cardiovascular telemedicine at Charite University in Berlin.

Why exclude patients with depression?



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Moral distress in ICU linked to physician burnout

BY TARA HAELE

MDedge News

REPORTING FROM CHEST 2018 ■

SAN ANTONIO – Understanding the experience of “moral distress” in critical care is essential because of its potential negative effects on health care providers and the need to prevent or address those effects, according to Marian Altman, PhD, RN, a clinical practice specialist from the American Association of Critical Care Nurses.

Dr. Altman spoke about moral distress as part of a panel discussion at the annual meeting of the American College of Chest Physicians on how to handle nonbeneficial treatment requests from families, including the legal and ethical obligations of care providers when a patient is receiving life-sustaining treatment.

“The key point about moral distress is that these are personal constraints, and so the choices of what is best for a patient often conflicts with what is best for the organization,” Dr. Altman told CHEST 2018 attendees. “It could conflict with what’s best for the care providers, the family, or even other patients, and so it’s that personal experience of moral compromise that often originates in this broader practice of our routine.”

While it does not necessarily occur frequently, moral distress is intense when it does occur.

“It really threatens the identity and the integrity of those who experience it because they truly believe they are seriously compromised with this deep personal effect,” Dr. Altman said.

Dr. Altman credited Andrew Jameton, a bioethicist who authored a seminal book on ethical issues in nursing in 1984, with defining exactly what moral distress is: “painful feelings and/or the psychological disequilibrium that



Dr. Marian Altman

occurs when a person is conscious of the morally appropriate action a situation requires but cannot carry out that action because of the institutionalized obstacles, such as lack of time, lack of supervisory support, exercise of medical power, and institutional policy or legal limits.” Or, in plainer terms, “Moral distress occurs when one knows the ethically correct action to take but feels powerless to take that action,” as Elizabeth G. Epstein, PhD, RN, and Sarah Delgado, MSN, RN, wrote in the *Online Journal of Issues in Nursing*.

To understand moral distress, it’s also important to know what it’s not, Dr. Altman said. It’s not the daily

stress of work or compassion fatigue or even burnout, though it can lead to burnout.

“Burnout is the state of physical, emotional, and mental fatigue and exhaustion caused by long-term involvement in situations that are emotionally demanding,” Dr. Altman said. “Burnout has been linked with moral distress, but they are two very different things.”

It’s also not a disagreement among colleagues or “an excuse to avoid a challenging situation.” In fact, the No. 1 cause of moral distress, in study after study, Dr. Altman said, is providing medical care, particularly medically futile care.

“Providing really unnecessary treatments and providing end-of-life care can lead to it as well as complex patients and challenging situations,” Dr. Altman said. Other causes include inadequate staffing, incompetent providers, poor communication, and advanced technology used to sustain life.

Though people often associate moral distress with intensive care, it can occur “wherever care is provided” and can “affect all members of the health care team,” Dr. Altman said. Though the early research into moral distress focused on critical care nurses, the field has since exploded, across all medical disciplines and in countries around the world.

That research has revealed how intensely moral distress can impact the psychological, biological, and social health of people. Physical symptoms that can result from moral distress include diarrhea, headache, heart palpitations, neck pain,

muscle aches, and vomiting. The emotions it rouses include frustration, fear, anger, anxiety, and, especially, powerlessness and guilt.

Moral distress can lead to burnout and dissatisfaction in individuals and, subsequently, reduced retention and productivity within institutions. Health care providers who experience moral distress may leave their position, their unit, or the profession altogether.

“That can have a huge impact in a time when we need many more health care providers to care for this exploding population,” Dr. Altman said. It can also negatively influence the patient-provider relationship, potentially affecting the quantity and safety of care delivered, she said.

But there are ways to address moral distress, she said.

“We’re not going to eradicate it because we will never eradicate critical care or end-of-life care, and those are the causes that lead to moral distress,” Dr. Altman said. “But what we can do, and what the research is now focusing on, is concentrate on improving our work environment, and help people recognize that they’re experiencing moral distress before it gets to burnout ... or mitigating moral distress when it occurs.”

Those improvements include fostering both a positive ethical environment, with ethics education, an ethics committee, and on-site ethics experts, and a healthy work environment with collaboration and skillful communication.

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Three-drug combo proves effective against multidrug-resistant ESBL-related urinary tract infections

BY JIM KLING

MDedge News

SAN FRANCISCO – A combination of ceftriaxone, a beta-lactamase inhibitor, and disodium ethylenediaminetetraacetic acid (EDTA) is superior to meropenem in the treatment of complicated urinary tract infections caused by extended-spectrum beta-lactamase (ESBL) gram-negative bacteria, according to a new study.

The post hoc analysis also found that the three-drug combination – known as CSE – is noninferior to meropenem in multidrug-resistant (MDR) and ceftriaxone-nonsusceptible (C-NS) pathogens.

CSE is aimed at the growing problem of antibiotic resistance, particularly the mechanisms used

by bacteria to counter beta-lactamase inhibitors. EDTA chelates zinc and calcium, and many of the resistance mechanisms rely on one or the other of these ions to function. In *in vitro* models, the combination of sulbactam and EDTA restores activity of ceftriaxone against various beta-lactamases.

Mohd Amin Mir, MD, head of clinical research at the Venus Medicine Research Center, Panchkula, India, and presenter of the study, said that, in the case of efflux pumps, “when there is EDTA present, it chelates the calcium, and that means there is no energy for the efflux pump to throw out the drug.”

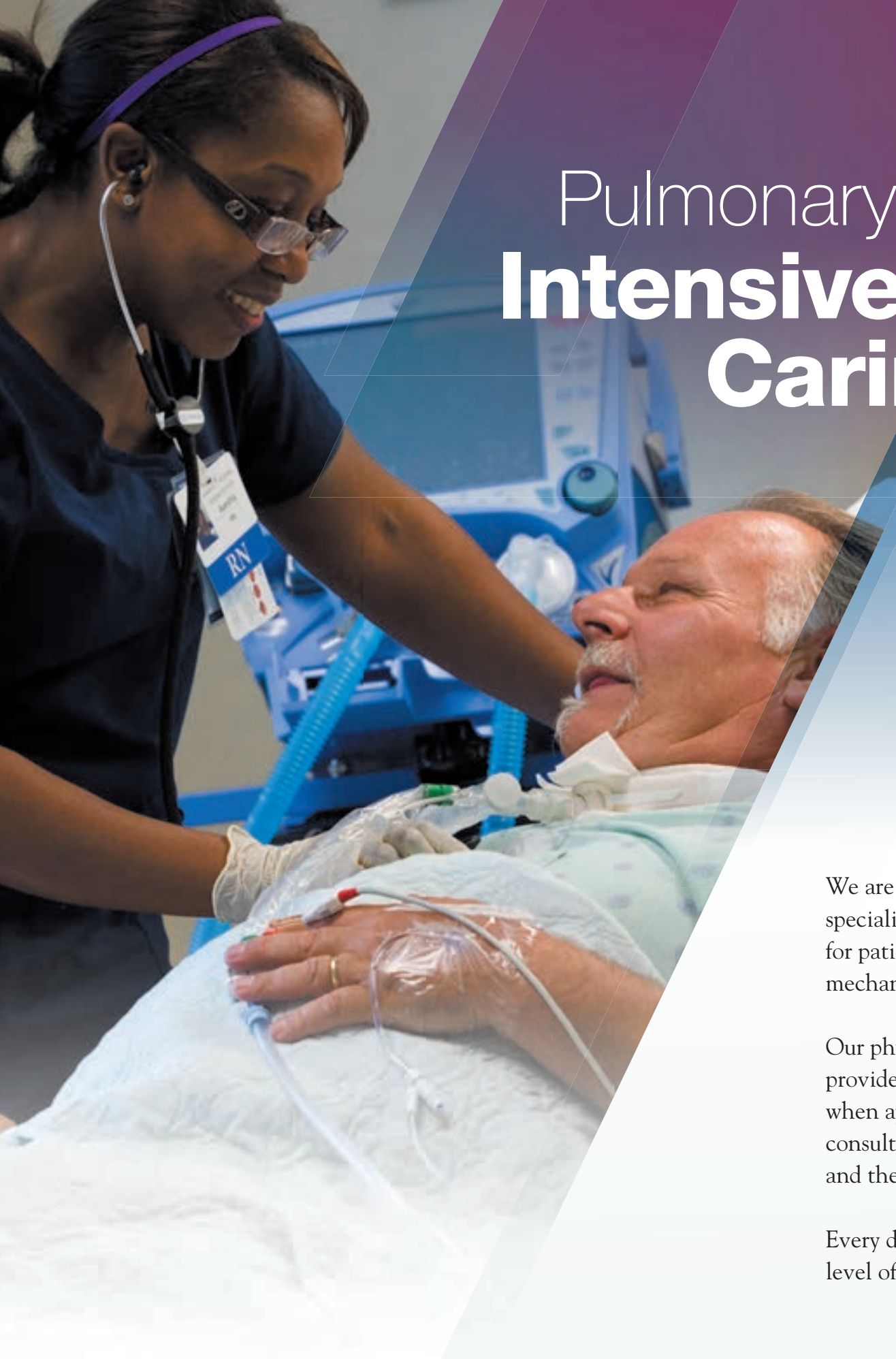
The penems, which include meropenem, are a class of synthetic antibiotics with an unsaturated beta-lactam ring. Like other antibiotics, they are

under assault from antibiotic resistance, especially beta-lactamase enzymes. “Penems are very precious drugs. The objective of developing [EDTA combinations] is to save the penems,” Dr. Mir said at an annual scientific meeting on infectious diseases.

The PLEA trial randomized 143 patients with complicated urinary tract infections or acute pyelonephritis to CSE (1 g ceftriaxone/500 mg sulbactam/37 mg EDTA) every 12 hours or 1 g meropenem (MR) as a 30-minute intravenous infusion over 30 minutes. Patients received treatment for 5-14 days.

The original study demonstrated that CSE is noninferior to meropenem at a 10% noninferiority margin. The researchers conducted a post hoc

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Antipsychotic drugs failed to shorten ICU delirium

BY BIANCA NOGRADY

MDedge News

The antipsychotic medications haloperidol and ziprasidone are no better than placebo in altering the duration of delirium in patients in intensive care, new research has found.

In a paper published in the *New England Journal of Medicine*, researchers reported the results of a randomized, double-blind, placebo-controlled trial in 566 patients with acute respiratory failure or shock and hypoactive or hyperactive delirium. Participants were randomized either to a maximum of 20 mg IV haloperidol daily, maximum 40 mg ziprasidone daily, or placebo.

At the end of the 14-day intervention period, the placebo group had a median of 8.5 days alive without delirium or coma, the haloperidol group had a median of 7.9 days, and the ziprasidone group had a median of 8.7 days. The difference between groups was not statistically significant.

There were also no significant dif-

ferences among the three groups in the secondary end point of duration of delirium and coma, 30-day and 90-day survival, time to freedom from mechanical ventilation, ICU discharge, ICU readmission, or hospital discharge.

Timothy D. Girard, MD, from the department of critical care at the University of Pittsburgh, and his coauthors wrote that their findings echoed those of two previous placebo-controlled trials in smaller numbers of ICU patients.

“One possible reason that we found no evidence that the use of haloperidol or ziprasidone resulted in a fewer days with delirium or coma than placebo is that the mechanism of brain dysfunction that is considered to be targeted by antipsychotic medications – increased dopamine signaling – may not play a major role in the pathogenesis of delirium during critical illness,” they wrote.

“In the current trial, approximately 90% of the patients received one or more doses of sedatives or analgesics, and the doses of sedatives and off-trial antipsychotic medica-



tions and the durations of exposures to those agents were similar in all trial groups,” the authors added.

Most of the patients in the trial had hypoactive delirium, which made it difficult to assess the effects of antipsychotics on hyperactive delirium.

The authors also commented that the patients enrolled were a mixed group, so their findings did not rule out the possibility that certain subgroups of patients – such as nonintubated patients with hyperactive delirium, those with alcohol withdrawal, or with other delirium phenotypes – may still benefit from antipsychotics.

Patients treated with ziprasidone were more likely to experience prolongation of the corrected QT interval. Two patients in the haloperidol group developed torsades de pointes but neither had received haloperidol in the 4 days preceding the onset of the arrhythmia.

One patient in each group – including the placebo group – experienced extrapyramidal symptoms and had treatment withheld. One

patient in the haloperidol group also had the trial drug withheld because of suspected neuroleptic malignant syndrome, but this was later ruled out, and one patient had haloperidol withheld because of dystonia.

The dose of haloperidol used in the study was considered high, the authors said, but they left open the possibility that even higher doses might help. However, they also noted that doses of 25 mg and above were known to have adverse effects on cognition, which is why they chose the 20-mg dosage.

The study was supported by the National Institutes of Health and the Department of Veterans Affairs Geriatric Research Education and Clinical Center. Most authors declared support from the NIH or VA during the course of the study. Four authors also reported fees and grants from private industry outside the context of the study.

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SOURCE: Girard TD et al. *N Engl J Med*. 2018 Oct 22. doi: 10.1056/NEJMoa1808217.

VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments: As with many conditions in critically ill patients, the etiologic factors leading to a given condition often are as varied as the condition itself. In the case of delirium, not only do patients present with very different forms, but the background leading up to the delirium can be quite heterogeneous (presence of baseline dementia, medication-induced, different levels of critical illness, toxic or metabolic factors, etc.). As a result, and as the authors mention, there may be certain subsets of patients that may benefit from a given treatment – and then there may be ones that are not helped or even harmed from the same treatment – simply given the nonuniform nature of critical care patients. This unavoidable feature of critical care research can lead to significant frustration when trying to design and interpret clinical research in the ICU.



Continued from page 32

analysis of patients who presented with complicated UTIs or acute pyelonephritis cases that were C-NS, ESBL-positive, or MDR pathogens. The researchers defined MDR as resistance to three or more categories of antimicrobial agents.

Of patients who received CSE, 97.3% had pathogens that were nonsusceptible to ceftriaxone, as did 98.6% of those who received MR; 85.1% of CSE and 81.2% of MR patients had an ESBL-producing pathogen; and 74.3% of infections in the CSE group were MDR, as were 65.2% of the MR group.

In all three resistant phenotypes, CSE at least trended to more favorable outcomes. In the MDR group, 96.4% of CSE patients achieved a clinical cure, compared with 88.9% in the MR group, and 94.5% achieved microbial eradication, compared with 86.75% in the MR group, the researchers found.

In the ESBL subgroup, 100% of patients in the CSE group achieved a clinical cure, compared with 89.3%, while 98.4% had complete eradication in the CSE group, compared with 87.5%. In the C-NS subgroup, 95.8% in the CSE group achieved a clinical cure, compared with 91.2%, and 94.4% achieved eradication,

compared with 89.7% in the MR group.

In the ESBL subgroup, the lower bound of the 95% confidence interval of the between-group difference was greater than 0, indicating superiority of CSE over MR for both clinical cure and eradication.

In the MDR and C-NS subgroups, CSE achieved noninferiority at a –10% margin.

CSE is currently commercially available in India, and the manufacturer is now seeking approval in Europe and the United States.

chestphysiciannews@chestnet.org

SOURCE: Mir MA et al. *IDWeek* 2018, Abstract 1959.

Palliative-rehab combo may improve QoL in newly diagnosed cancer patients

BY ANDREW D. BOWSER

MDedge News

In patients with a new diagnosis of advanced cancer, an intervention that combined palliative care with rehabilitation helped improve quality of life, results of a randomized, single-center study suggest.

Patients had a significant improvement in their most pressing quality-of-life issues after participating in the intervention, which included individualized palliative care consultations and a patient/caregiver “school” of lectures, discussion, and physical exercise, investigators said.

These findings suggest that every patient facing an advanced cancer diagnosis should at least have an initial exploratory consultation with a specialized palliative care team, and should be offered not only the usual components of palliative care, but also cancer rehabilitation, said Lise Nottelmann, MD, of the department of oncology at Vejle Hospital in Denmark.

“We should be active as a health care system in approaching these patients and offering them this intervention, or at least a consultation exploring these aspects of quality of life,” Dr. Nottelmann said in an interview at the 2018 Palliative and Supportive Care in Oncology Symposium.

The study by Dr. Nottelmann and her colleagues, presented at the symposium, comprised 301 patients with nonresectable solid tumors, including lung, gastrointestinal, prostate, and others. Those patients

were randomly allocated to the palliative rehabilitation intervention or to standard care only.

Every patient participated in two consultations with a specialized palliative care team, and then had the opportunity for individualized contact with the team in a 12-week open contact period. They were also invited to participate in the school sessions, each of which included a 20-minute lecture on topics such as physical activity and good nutrition plus a 40-minute discussion period, followed by an exercise session.

Of the patients randomized to the palliative rehabilitation intervention, 26 participated only in the initial consultations, while 59 participated in the group program, and 47 had individual consultations, Dr. Nottelmann reported.

To measure quality of life, the investigators asked patients to identify a “primary problem” that corresponded to 1 of 12 scales in the EORTC QLQ-C30 questionnaire related to physical and role functioning, emotional and cognitive functioning, or symptoms.

The primary endpoint of the analysis was improvement in QLQ-C30 scores at 12 weeks. The analysis was done on specific scales in the patients who identified a primary problem, combined with global QLQ-C30 scores for the remaining one-quarter of the patients who did not, Dr. Nottelmann said.

After 12 weeks, the patients in the intervention arm had a significant improvement versus the no-intervention arm as measured by a version of the EORTC QLQ-C30

questionnaire. The absolute between-group difference in scores was 3.0 (95% confidence interval, 0.0-6.0; *P* less than .047), according to researchers.

Starting palliative care earlier in the course of cancer, as done in this

“We should be active as a health care system in approaching these patients and offering them this intervention, or at least a consultation exploring these aspects of quality of life.”

intervention, is an increasingly accepted practice, supported by large studies and recent clinical practice guidelines that recommend early integration of palliative care into the seriously ill patient’s care plan.

What was different about this intervention was the integration of rehabilitation aspects into palliative

care, Dr. Nottelmann said in the interview. While not traditionally thought of as a component of palliative care, the concept of palliative rehabilitation is gaining ground, she said.

The goal of rehabilitative palliative care is to help individuals with life-limiting or terminal conditions actively self-manage their conditions so they can “live fully” and enjoy the best quality of life possible, according to Hospice UK, a national charity for hospice care in the United Kingdom.

The symposium was cosponsored by AAHPM, ASCO, ASTRO, and MASCC. Dr. Nottelmann and her colleagues reported research funding from the Danish Cancer Society. Dr. Nottelmann had no disclosures related to the presentation. One co-author provided disclosures related to Roche, Amgen, Bayer, and Merck Sharp & Dohme.

chestphysiciannews@chestnet.org

SOURCE: Nottelmann L et al. PallOnc 2018, Abstract 75.

ALEX: Alectinib showed superior CNS efficacy in ALK+ NSCLC

BY AMY KARON

MDedge News

For patients with treatment-naive anaplastic lymphoma kinase-positive (ALK+) non-small cell lung cancer (NSCLC), twice-daily oral treatment with alectinib (600 mg) was associated with significantly greater activity in the CNS and significantly delayed CNS progression, compared with crizotinib (200 mg), based on secondary analyses from the pivotal phase 3 ALEX trial.

Time to CNS progression was significantly longer with alectinib versus crizotinib (hazard ratio, 0.18; 95% confidence interval, 0.09-0.36) regardless of whether patients had asymptomatic baseline CNS metastases or a prior history of radiotherapy.

For patients with baseline asymptomatic CNS metastases, the 12-month cumulative incidence of CNS progression was 16% with alectinib versus 58.3% with crizotinib.

Continued on following page

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Continued from previous page

Among patients without asymptomatic CNS metastases at baseline, these rates were 4.6% versus 31.5%, respectively.

The findings “consolidate alectinib as the standard of care for untreated, advanced ALK+ NSCLC, irrespective of the presence or absence of baseline CNS metastases,” Shirish M. Gadgeel, MD, of the University of Michigan, Ann Arbor, and his associates wrote in *Annals of Oncology*.

ALEX was the first study of an ALK inhibitor to include a prospective, standardized intention-to-treat analysis of CNS lesions, regardless of whether patients had these lesions at baseline. All patients underwent brain imaging at baseline and every 8 weeks thereafter.

In the primary analysis of 303 patients, alectinib significantly improved progression-free survival (PFS) in patients with and without baseline CNS disease and showed a significantly higher intracranial overall response rate, irrespective of whether patients had previously received radiotherapy.

Based on these results, National Comprehensive Cancer Network guidelines were updated to include a category 1 recommendation for the first-line use of alectinib in patients with ALK+ NSCLC.

The current analysis focused on CNS efficacy. In all, 122 patients had CNS metastases at baseline. Progression-free survival was similar regardless of whether patients had brain lesions (HR, 0.40; 95% CI, 0.25-0.64) or not (HR, 0.51; 95% CI, 0.33-0.80; $P = .36$). History of radiotherapy also did not

significantly affect overall CNS response or progression-free survival.

“Our data are in agreement with a pooled analysis of alectinib phase 2 trials, which demonstrated that CNS efficacy of alectinib is maintained regardless of radiotherapy history in crizotinib-pretreated patients,” the investigators wrote.

“Our data are in agreement with a pooled analysis of alectinib phase 2 trials, which demonstrated that CNS efficacy of alectinib is maintained regardless of radiotherapy history in crizotinib-pretreated patients.”

Because ALEX excluded patients with symptomatic CNS disease, its effects in this population remain unclear, the investigators noted. “ALEX data strongly suggest that in asymptomatic patients, treating CNS metastases with alectinib alone may result in a reduced or delayed need for local CNS treatment.”

F. Hoffman-La Roche funded the study. Dr. Gadgeel reported honoraria and consultancy fees from Roche/Genentech, ARIAD Pharmaceuticals, AstraZeneca, Bristol-Myers Squibb, and Pfizer.

chestphysiciannews@chestnet.org

SOURCE: Gadgeel SM et al. *Ann Oncol*. 2018 Sep 12. doi: 10.1093/annonc/mdy405.

VIEW ON THE NEWS

M. Patricia Rivera, MD, FCCP, comments: ALK gene rearrangements are identified in about 3%-7% of patients with advanced NSCLC. Crizotinib has been the standard treatment in these patients with improved progression-free survival (PFS), objective response rates (ORR), and symptom improvement compared with chemotherapy. Unfortunately, the majority of patients with ALK-positive NSCLC treated with crizotinib will develop resistance mutations that lead to progression of disease, most commonly with brain metastases. Prognosis of CNS metastasis is poor (median overall survival reported to be about 3 months) and the efficacy of crizotinib in treating CNS metastases is limited by decreased blood-brain barrier penetration. Alectinib, a second-generation ALK inhibitor, results in significant improvement in PFS by 47%. Not only did alectinib extend the time that the patients lived without worsening of disease, it significantly reduced the risk of CNS metastases and was associated with a better toxicity profile compared to crizotinib. The results of this study established alectinib as a more suitable drug in the first-line treatment for ALK-positive NSCLC.



Nasal cannula device may be an option for severe COPD

BY TED BOSWORTH

MDedge News

PARIS – As an alternative to noninvasive ventilator devices (NIV), a battery-powered high-flow nasal cannula delivering heated air improves exercise tolerance as measured with the 6-minute walking distance (6MWD), according to a crossover trial presented at the annual congress of the European Respiratory Society.

“In a population with very severe dyspnea as a cause of exercise limitations, the high-flow nasal cannula significantly improved 6MWD without worsening dynamic hyperinflation,” reported Veronica Rossi, a pulmonary rehabilitation specialist at the IRCCS Istituti Clinici Scientifici Salvatore Maugeri, Pavia, Italy.

Not least important, these preliminary results show treatment with the device to be well tolerated, a potential advantage over NIV, according to Ms. Rossi, who cited published studies suggesting up to 35% of patients are intolerant to ambulatory NIV therapy.

In the study, 12 clinically stable COPD patients with a 6MWD of less than 300 m and dyspnea at a low level of exertion were enrolled. In random order on 2 consecutive days, patients were evaluated with the 6MWD test while fitted with the high-flow nasal cannula (HFNC) or while breathing room air.

The HFNC device delivers heated and humidified oxygen, which has been previously shown by the same group to improve oxygen saturation



MS. ROSSI

(Respir Med. 2016;118:128-32). In this study, the oxygen fraction (FiO₂) of the air delivered by the proprietary HFNC device, marketed under the name AIRVO2 (Fisher & Paykel), was the same as the room air during the control exam.

In both tests, the patients performed the 6MWD while pushing a cart holding the device and the battery power source.

The mean 6MWD was 306 m using HFNC versus 267 m during the control test (*P* less than .05), even though the mean and nadir blood oxygenation (SpO₂) levels were the same. However, the postexercise respiratory rate was significantly lower (*P* less than .05) when HFNC was used, Ms. Rossi reported. The inspiratory capacity was unchanged.

The improved levels of oxygen saturation (SaO₂) demonstrated previously with high flows of humidified oxygen provided the basis for this preliminary crossover study, but a larger multicenter randomized trial was initiated last year. In that study with a planned enrollment of 160 COPD patients, the comparison will be between HFNC and usual oxygen delivered by a venturi mask. The primary outcome of the study, which will be completed early in 2019, is endurance improvement.

“COPD patients with severe dyspnea are frequently unable to achieve a workload that leads to improved exercise tolerance, with a result of reduced daily physical activities,” Ms. Rossi explained. She indicated that the HFNC, which is now being evaluated at several institutions, might be an important alternative to NIV in permitting patients to achieve adequate mobility.

The device is likely to be improved with technological advances, according to Ms. Rossi. She acknowledged that the current battery is heavy and the duration of the charge is relatively short,

VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments:

High-flow nasal cannula devices have led to remarkable changes in the care of critically ill acute respiratory failure patients and have been demonstrated to prevent intubation and re-intubation in several types of ICU populations. The physiologic effects of this device have been



shown to go well beyond an “oxygen delivery” system, and some may argue that its benefits are derived more from its improvements in work of breathing, ventilation distribution, and reduction of physiologic dead space. As such, this system may be well-suited for the pulmonary rehabilitation setting as it may reduce respiratory muscle fatigue and lessen ventilation heterogeneity (especially as exercise intensity and respiratory frequency increase). Less attention on oxygenation is needed, as these physiologic effects would likely benefit most of these patients, irrespective of their blood oxygen levels.

but she characterized this device as “good fit” for patients with very severe COPD. Only 8% of patients failed to complete this study.

Dr. Rossi reports no financial relationships relevant to this study.

chestphysiciannews@chestnet.org

CT scanning for evaluating pulmonary embolism overused

BY ANDREW D. BOWSER

MDedge News

REPORTING FROM CHEST 2018 ■

SAN ANTONIO – The recommended approach to evaluating suspected pulmonary embolism is “greatly underutilized” in the Veterans Health Administration system, Nancy Hsu, MD, said at the annual meeting of the American College of Chest Physicians.

Most Veterans Affairs sites did not require incorporation of a clinical decision rule (CDR) and highly sensitive D-dimer prior to ordering CT pulmonary angiography (CTPA) for suspected pulmonary embolism (PE), according to results of a survey by Dr. Hsu and her coinvestigator, Guy Soo Hoo, MD.

While CTPA has become the imaging modality of choice for evaluating suspected PE, it is overused and potentially avoidable in one-third of

cases, said Dr. Hsu, who is with the VA Greater Los Angeles Healthcare System.

“In the 10 years following the advent of CTPA use, there was a 14-fold increase in usage, but there was no change in mortality,” Dr. Hsu said. “This is consistent with overdiagnosis.”



DR. HSU

Indiscriminate use of CTPA results in unnecessary and avoidable radiation exposure, contrast-related reactions, and treatment-related bleeding, Dr. Hsu said.

Dr. Hsu and Dr. Soo Hoo surveyed 606 individuals at 18 Veterans Integrated Service Networks (VISNs) and 143 medical centers. A total of 120 fully completed ques-

tionnaires were analyzed.

Most respondents (63%) were chiefs, and 80% had 11+ years of experience, Dr. Hsu reported.

Almost all respondents (85%) said CDR with or without D-dimer was not required before ordering a CTPA, survey results show, while only about 7% required both.

“A very small minority of [Veterans Integrated Service Networks], or geographic regions, contained even one hospital that adhered to the guidelines,” Dr. Hsu added.

Though further analysis was limited by sample size, the average CTPA yield for PE appeared to be higher when both components were used in the evaluation, according to Dr. Hsu, who noted an 11.9% yield for CDR plus D-dimer. Use of CTPA appeared lower at sites with CDR and D-dimer testing, Dr. Hsu added.

These results suggest a need for further research to compare CTPA

use and yield in sites that have the algorithm in place, Dr. Hsu told attendees at the meeting.

Adherence to the CDR plus D-dimer diagnostic strategy is “modest at best” despite being a Top 5 Choosing Wisely recommendation in pulmonary medicine, said Dr. Hsu.

The biggest barrier to optimal practice may be the fear of a patient who “falls through the cracks” based on false-negative CDR and D-dimer data, according to Dr. Hsu.

On the other hand, judicious use of CTPA likely avoids negative sequelae related to radiation, contrast exposure, and treatment-related bleeding, Dr. Hsu said.

Dr. Hsu and Dr. Soo Hoo disclosed that they had no relationships relevant to their research.

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SOURCE: Hsu N et al. CHEST 2018 Oct. doi: 10.1016/j.chest.2018.08.937.

Reprocessed bronchoscopes found to harbor microbial growth and biocontamination

BY ANDREW D. BOWSER

MDedge News

FROM THE JOURNAL CHEST® ■

Bronchoscope reprocessing was ineffective for eliminating all residual biocontamination even when done in accordance with endoscope reprocessing standards, according to results of a prospective, multisite investigation.

All clinically used bronchoscopes evaluated in the study had residual

maintenance guidelines are needed, along with quality management programs to ensure that these complex processes are carried out effectively," Ms. Ofstead and her colleagues said in their report.

Institutions also should consider shifting from high-level disinfection (HLD) to sterilization to reduce patient exposure to contaminated bronchoscopes, they added.

The study was conducted in three large, tertiary hospitals that con-

"Evidence-based, bronchoscope-specific reprocessing and maintenance guidelines are needed, along with quality management programs to ensure that these complex processes are carried out effectively."

contamination after reprocessing, and more than half showed microbial growth, the researchers reported in the journal CHEST.

These findings suggest that systematic changes are needed to improve cleaning and disinfection and to avoid the retention of bioburden, said researcher Cori L. Ofstead, MSPH, and her coinvestigators (Chest. 2018 Nov;154[5]:1024-34).

"Evidence-based, bronchoscope-specific reprocessing and

tributed a total of 24 clinically used devices. That total comprised nine therapeutic, nine pediatric, and six endobronchial ultrasound (EBUS) bronchoscopes that were all reprocessed in accordance with each institution's standard practices.

Proteins were detected in 100% of the bronchoscopes after HLD, according to researchers.

Looking at 20 paired postcleaning and post-HLD samples, the researchers found microbial growth in 11 of 20 (55%) manually cleaned bronchoscopes and 14 of 24 (58%) bronchoscopes after HLD. The post-HLD samples included mold and recognized pathogens such as *Escherichia coli*, as well as normal flora and environmental bacteria, they said.

All 24 of the bronchoscopes had visible irregularities, including brown, red, or oily residue; retained fluid; debris in channels; scratches; or damage at insertion tubes and distal ends, they added.

Substandard reprocessing practices were found at two of the three participating insti-

VIEW ON THE NEWS

Dismaying observations warrant prompt action

Results of this study, which document biological contamination of inadequately reprocessed bronchoscopes, are provocative and "alarming," warranting attention from physicians, paramedical staff, administrators, and manufacturers, Atul C. Mehta, MBBS, and Thomas Gildea, MD, wrote in an editorial (Chest. 2018 Nov;154[5]:1001-3).

A breach in the disinfection protocol is the "most common culprit" behind the spread of infection during bronchoscopy, they noted.

"In our opinion, the interventional pulmonology community has buried its head in the sand regarding this issue," they wrote.

While cases of true infection related to bronchoscopy "can seldom be differentiated" in the literature, it is nevertheless "mandatory" that biologic contamination from one patient to another be avoided, they wrote.

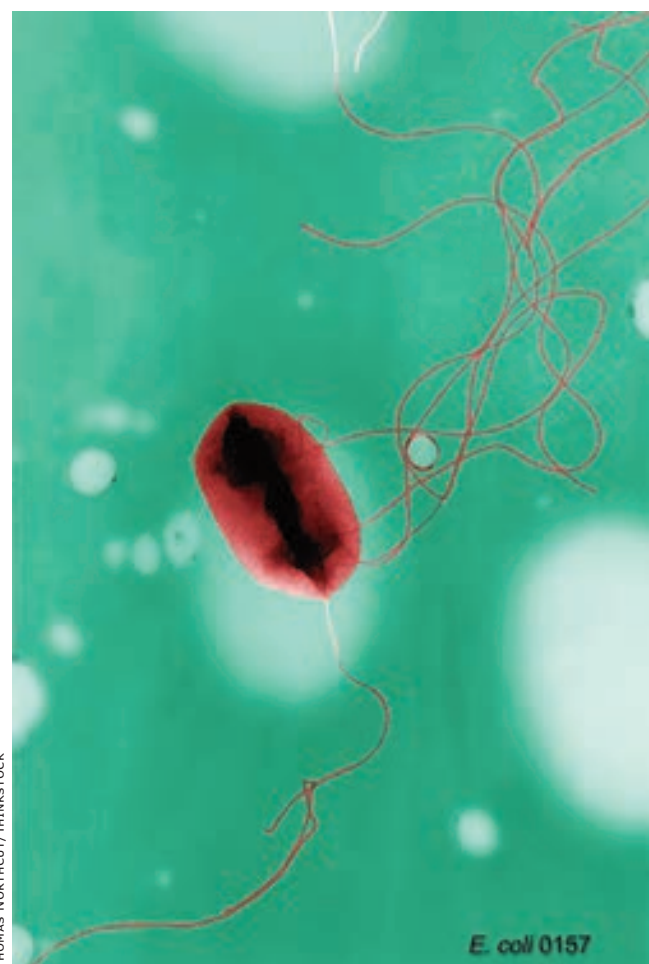
One dismaying observation in the present study is that human proteins were detected in the working channels of all of bronchoscopes after high-level disinfection (HLD), Dr. Mehta and Dr. Gildea stated.

"It is critical that if HLD remains the standard of care and is sufficient, it must be done properly," they wrote. "This study raises concerns that HLD itself may not be sufficient, and we have no options for disposable specialty bronchoscopes."

Unfortunately, requiring sterilized bronchoscopes is time-consuming and impractical for a busy bronchoscopy practice, according to the authors, while disposable bronchoscopes need to be established as clinically effective and cost effective.

In the meantime, the authors recommended that clinicians proactively consider initiatives to ensure patient safety, including formally assessing HLD processes, examining all bronchoscopes for visible damage, and ensuring that HLD guidelines are met or exceeded.

Dr. Mehta and Dr. Gildea are with the department of pulmonary medicine at Cleveland Clinic. Neither author reported conflicts of interest related to the editorial, which was published in Chest.



tutions, according to the investigators. At one site, technicians reused syringes to flush channels with alcohol stored in an uncovered bowl during the day, according to the report, and bronchoscopes at that site were dried with reused towels and stored in a cabinet without active ventilation.

"Nursing staff were observed handling patient-ready bronchoscopes with bare hands," the investigators reported.

Although clinical outcomes were not measured, the contamination, microbial growth, and defects observed in this study are "worrisome," according to authors, because of the high infection risk in many patients undergoing bronchoscopy, and because of the infectious outbreaks and patient deaths linked to contaminated bronchoscopes in previous investigations.

Research funding for the study was provided by 3M Company.

Study materials were provided by 3M Company and Healthmark Industries. Ms. Ofstead and several coauthors reported employment with Ofstead & Associates, which has received research funding and speaking fees related to infection prevention from 3M Company, Healthmark Industries, Advanced Sterilization Products (Johnson & Johnson), and others.

The senior author of the study was J. Scott Ferguson, MD, of the division of pulmonary and critical care medicine at the University of Wisconsin School of Medicine and Public Health, Madison. Dr. Ferguson provided disclosures related to NewWave Medical, Pharmaceutical Product Development, Oncocyte, Concordia, and PneumRx.

chestphysiciannews@chestnet.org

SOURCE: Ofstead CL et al. Chest. 2018 Nov;154(5):1024-34.

Genetic risk factor found for RA-associated interstitial lung disease

BY BRUCE JANCIN

MDedge News

CHICAGO – Rheumatoid arthritis-associated interstitial lung disease and idiopathic pulmonary fibrosis without RA share a common genetic underpinning whose hallmark is a gain-of-function MUC5B gene promoter variant that cranks up mucin production in the lungs, Pierre-Antoine Juge, MD, reported at the annual meeting of the American College of Rheumatology.

He presented a seven-country genetic case-control study of 620 patients with RA-associated interstitial lung disease (RA-ILD), 614 with RA but no ILD, and 5,448 unaffected controls. The key finding was that the MUC5B promoter variant rs35705950, already known to be the strongest genetic risk factor for idiopathic pulmonary fibrosis (IPF), also contributes substantially to the risk of RA-ILD.



Dr. Pierre-Antoine Juge

Indeed, the presence of the MUC5B promoter variant in patients with RA proved to be associated with substantially higher risk of RA-ILD than the previously recognized risk factors for RA-ILD, including cigarette smoking and the human leukocyte antigen locus for RA, according to Dr. Juge, a rheumatologist at Bichat Hospital-Claude Bernard and Paris Diderot University.

MUC5B encodes for mucin production in the lungs. The increased risk of RA-ILD conferred by the presence of the MUC5B promoter variant was confined to the 41% of RA-ILD patients with a pattern of usual interstitial pneumonia (UIP) or possible UIP on high-resolution CT. The presence of the MUC5B promoter variant in RA patients was independently associated with an adjusted 6.1-fold increased risk of ILD with a UIP pattern on imaging – marked by honeycombing, reticular abnormalities, and subpleural involvement – compared with RA patients who didn't possess the gain-of-function MUC5B variant. The risk of other types of RA-ILD wasn't affected by the presence or absence of the MUC5B variant.

These findings have potentially important implications for clinical practice, given that clinically significant ILD is present in about 10% of all RA patients and occult ILD is detect-

able using high-resolution CT in up to half of individuals with RA, Dr. Juge observed. Detection of the MUC5B promoter variant could be used to screen patients with RA for preclinical ILD. Also, there is now a sound rationale to study drugs known to be effective for IPF as potential treatments for RA-ILD, he said.

Dr. Juge reported having no financial conflicts regarding the study, which was sponsored by the National Institutes of Health, the U.S. Department of Defense, the French Rheumatology Society, the Japanese Society for the Promotion of Science, Fondation Arthritis, and the Nina Ireland Program for Lung Health.

The study was published online in the *New England Journal of Medicine* (doi: 0.1056/NEJMoa1801562).

bjancin@mdedge.com

SOURCE: Juge P-A et al. *Arthritis Rheumatol.* 2018;70(Suppl 10), Abstract 1819.

Updated IPF guideline refines diagnostic criteria with HRCT

BY WILL PASS

MDedge News

A recently updated guideline for idiopathic pulmonary fibrosis (IPF) provides refined diagnostic criteria in an effort to improve clinical application and diagnostic accuracy.

Of note, the guideline recommends that high-resolution CT (HRCT) patterns be used to dictate management course. The guideline also calls for detailed medical history, serological testing to exclude connective tissue disease, and multidisciplinary discussion. Serum biomarkers are recommended against as a means of distinguishing between IPF and other interstitial lung diseases (ILDs).

“Diagnosing IPF is challenging because these symptoms are nonspecific: They occur with all other interstitial lung diseases and with other respiratory problems,” Ganesh Raghu, MD, chair of the guideline committee and professor of medicine and director of the Center for Interstitial Lung Disease at the University of Washington, Seattle, said in a written statement. “Because drugs may slow the progression of IPF, an early and accurate diagnosis is essential for prompt and appropriate treatment for this fatal disease.”

The 2018 guideline represents a second collaborative effort from the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society. The guideline committee consisted of 29 clinicians, scientists, and a patient with IPF. They evaluated all IPF-related evidence and rated the quality of findings with the GRADE (Grading

of Recommendations, Assessment, Development, and Evaluation) system. The first IPF guideline was published 7 years ago; the intervening time has revealed some clinical limitations that the 2018 guideline aims to fix.

“The 2011 guideline provided the first evidence-based, formal criteria for diagnosis of IPF and allowed patients with a well-defined diagnosis of IPF to participate in numerous clinical studies and randomized controlled trials that enhanced our understanding of the disease,” Dr. Raghu said. “However, it became clear that there were significant challenges in ascertaining the diagnosis per the 2011 criteria, and abundant evidence accumulated since then allowed the committee to refine the diagnostic criteria now.”

“This [updated] guideline is intended to help clinicians make an accurate diagnosis of IPF,” the authors wrote in the *American Journal of Respiratory and Critical Care Medicine*, “and to empower them to implement recommended courses of action in the context of individual patient values and preferences, particularly decisions regarding which diagnostic interventions to pursue.”

While the 2011 guideline did not distinguish between patients with different HRCT patterns, the 2018 guideline emphasizes the use of HRCT. It is now recommended that patients undergo HRCT to determine the pattern of usual interstitial pneumonia (UIP). Broadly, patients exhibit the UIP pattern or one of three possible non-UIP patterns (probable UIP, indeterminate UIP, or an alternative diagnosis). Patients with probable UIP, indeterminate UIP, or an alternative diagnosis

should undergo bronchoalveolar lavage (BAL) and surgical lung biopsy (SLB). Transbronchial lung biopsy (TBBx) and lung cryobiopsy recommendations were not described in these patients because of a lack of evidence. However, patients with UIP should not undergo BAL, SLB, TBBx, or cryobiopsy.

For all patients, the 2018 guideline recommends that medical histories include environmental exposure and medication use, and that serological testing is performed to exclude connective tissue disease. The authors reported funding from Bellerothon, Gilead, Roche, Sanofi, and others.

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SOURCE: Raghu G et al. *Am J Respir Crit Care Med.* 2018 Sep 1. doi: 10.1164/rccm.201807-1255ST.



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Next-gen triple correctors look promising for CF

BY ANDREW D. BOWSER

MDedge News

Adding a next-generation corrector to dual corrector–potentiator therapy is safe and effective in cystic fibrosis patients with one or two Phe508del alleles, results of two randomized phase 2, proof-of-concept clinical trials suggest.

The two trials, which evaluated the use of VX-445 or VX-659, respectively, in combination with tezacaftor-ivacaftor (Symdeko), were reported in the *New England Journal of Medicine*.

Both triple combinations improved lung function for patients heterozygous for the Phe508del cystic fibrosis transmembrane conductance regulator (CFTR) mutation and a minimal function mutation (Phe508del-MF) who had not previously received CFTR modulators, according to the investigators, who reported results simultaneously at the North American Cystic Fibrosis Conference in Denver.

These therapies also were effective in patients homozygous for Phe508del CFTR mutation (Phe508del-Phe508del) who had previously been treated with tezacaftor-ivacaftor, the results show.

No dose-limiting side effects or toxic effects were observed in the phase 2 studies, which included 4-week treatment periods.

“These trials provide proof of the concept that targeting the Phe508del CFTR protein with a triple-combination corrector–potentiator regimen can restore CFTR function and has the potential to represent

a clinical advance for patients with cystic fibrosis who harbor either one or two Phe508del alleles, approximately 9 of every 10 patients with the disease,” Steven M. Rowe, MD, of the University of Alabama at Birmingham and his coauthors said in the report on VX-659 phase 2 study.



DR. ROWE

In that report, 63 patients with the Phe508del-MF genotype were randomized to one of three VX-659 doses in combination with tezacaftor and ivacaftor versus triple placebo for 4 weeks, while 29 Phe508del-Phe508del patients underwent a 4-week tezacaftor-ivacaftor run-in phase before starting 4 weeks of the triple combination.

The primary efficacy endpoint of the study was the absolute increase in percentage of predicted forced expiratory volume in 1 second (FEV₁).

In the Phe508del-MF patients, adding VX-659 improved that endpoint by up to 13.3 points versus baseline (*P* less than .001), whereas the absolute change was just 0.4 in the placebo group, the report shows. In the Phe508del-Phe508del group, there was a 9.7-point increase over baseline.

Similarly, the companion study on VX-445, reported by Jennifer L. Taylor-Cousar, MD, of National Jewish Health, Denver, and her colleagues, showed an increase in percentage of predicted FEV₁ of up to 13.8 points for Phe508del-MF patients (*P* less than .001), and an increase of 11.0

points in the Phe508del-Phe508del group (*P* less than .001).

Those results suggest that targeting the Phe508del CFTR mutation with a combination of two correctors and a potentiator can produce effective CFTR function in patients who have these forms of cystic fibrosis, according to Dr. Taylor-Cousar and her colleagues.

“Lung function was improved by a magnitude similar to that achieved with the CFTR modulator ivacaftor in patients with gating mutations, in whom treatment has been disease modifying,” the researchers wrote in their report.

Sweat chloride concentrations were reduced and respiratory domain scores were improved in patients receiving triple therapy.

Triple therapy improved Phe508del CFTR protein processing and trafficking, and chloride transport more so than any two agents in combination, according to in vitro results, also described in the studies.

Phase 3 trials of these compounds are now underway, they said.

Both studies were supported by Vertex Pharmaceuticals, which received funding from the Cystic Fibrosis Foundation for the development of both VX-445 and VX-659. Dr. Rowe and Dr. Taylor-Cousar reported grants, personal fees, and nonfinancial support from Vertex while conducting the study. Study authors also reported disclosures related to AstraZeneca, Novartis, Bayer, Proteostasis, Gilead, Galapagos/AbbVie, and Celtaxsys, among other entities. Full disclosures for all authors were provided in the journal.

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VIEW ON THE NEWS

Daniel Ouellette, MD, FCCP, comments: The two beautiful girls died decades ago, when they were teenagers, from cystic fibrosis (CF). They were my nieces.



New therapies are emerging to treat CF. Recent reports suggest that the addition of a next-generation corrector to dual corrector–potentiator therapy will help restore CFTR function. Ninety percent of CF patients may be candidates for this treatment. Adult pulmonologists have seen only occasional CF patients, and have long regarded cystic fibrosis as a condition treated by their pediatric colleagues. If improved clinical outcomes are associated with the use of these new drugs, adult pulmonologists will see a new population of patients in their clinics: cystic fibrosis patients living adult lives. I, for one, would welcome this work and its challenges.

SOURCES: Keating D et al. *N Engl J Med*. 2018 Oct 18. doi: 10.1056/NEJMoa1807120; Davies JC et al. *N Engl J Med*. 2018 Oct 18. doi: 10.1056/NEJMoa1807119.

FDA approves omadacycline for pneumonia

BY CHRISTOPHER PALMER

MDedge News

The Food and Drug Administration has approved omadacycline (Nuzyra), a tetracycline antibiotic, for treating community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI) in adults, the manufacturer, Paratek, announced in a press release.

The company expects that omadacycline will be available in the first quarter of 2019. Administered once-daily in either oral or IV formulations, the antibiotic was effective and well tolerated across multiple trials, which altogether included almost 2,000 patients, according to Paratek. As part of the approval, the company has agreed to conduct postmarketing studies, specifically,

more studies in CABP and in pediatric populations. “To reduce the development of drug-resistant bacteria and maintain the effectiveness of Nuzyra and other antibacterial drugs, Nuzyra should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria,” according to a statement in the indications section of the prescribing information.

Omadacycline is contraindicated for patients with a known hypersensitivity to the drug or any members of the tetracycline class of antibacterial drugs; hypersensitivity reactions have been observed, so use should be discontinued if one is suspected. Use of this drug during later stages of pregnancy can lead to irreversible discoloration of the infant’s teeth and inhibition of bone growth; it should also not be used during breastfeeding.

Because omadacycline is structurally similar to tetracycline class drugs, some adverse reactions to those drugs may be seen with this one, such as photosensitivity, pseudotumor cerebri, and antianabolic action. Adverse reactions known to have an association with omadacycline include nausea, vomiting, hypertension, insomnia, diarrhea, constipation, and increases of alanine aminotransferase, aspartate aminotransferase, and/or gamma-glutamyl transferase.

Drug interactions may occur with anticoagulants, so dosage of those drugs may need to be reduced while treating with omadacycline. Antacids also are believed to have a drug interaction – specifically, impairing absorption of omadacycline.

cpalmer@mdedge.com

NAMDRC update

BY PHIL PORTE

Executive Director, NAMDRRC

NAMDRRC focuses on keeping its members informed on legislative and regulatory issues impacting their practices.

NAMDRRC's mission statement clearly signals its commitment -- **to improve access to quality care for patients with respiratory disease by removing regulatory and legislative barriers to appropriate treatment.** Adhering to that commitment presents challenges in the rapidly changing structure of the delivery of health care. For example, 10 years ago, the majority of NAMDRRC members were private practitioners/group practices, many with contracts to provide a range of services to institutions. While those agreements varied, the underlying principles were relatively constant -- structure your agreements that were mutually beneficial to physician and hospital.

Today, those agreements have been replaced by employment contracts or simply disappeared entirely, replaced by various business models that have invariably shifted the focus of coverage and payment issues away from the group practice into significantly different financial incentives. The challenge for NAMDRRC is to keep its members informed about struc-

tural changes in coverage and payment rules that could impact their decision making. In November 2018, CMS published three distinctly separate sets of rules slated to take effect in 2019, all of which affect physicians in the pulmonary, critical care, and sleep landscapes. Through the monthly membership publication, the Washington Watchline, members get timely

NAMDRRC's mission statement clearly signals its commitment to improve access to quality care for patients with respiratory disease.

information that impact their practices. Excerpts from a recent Watchline include:

Physician fee schedule: As most physicians know, CMS had proposed dramatic changes to payment for Level 4 and Level 5 E&M codes, but due to strong reaction from many within the medical community, CMS is withdrawing that specific proposal, at least in the short term. Related provisions include:

- For CY 2019 and 2020, CMS will continue the current coding and payment structure for E/M office/outpatient visits,
- Effective January 1, 2019, for new and established patients for E/M office/outpatient visits, practitioners need not re-enter in the medical record information on the patient's chief complaint and history that has already been entered by ancillary staff or the beneficiary. The practitioner may simply indicate in the medical record that he or she reviewed and verified this information.
- For 2021, CMS is finalizing a significant reduction in the current

payment variation in office/outpatient E/M visit levels by paying a single rate for E/M office/outpatient visit levels 2, 3, and 4 (one for established and another for new patients) beginning in 2021. However, CMS is not finalizing the inclusion of E/M office/outpatient level 5 visits in the single payment rate, to better account for the care and needs of particularly complex patients.

- CMS policy for 2021 will adopt add-on codes that describe the additional resources inherent in visits for primary care and particular kinds of specialized medical care. As discussed further below, these codes will only be reportable with E/M office/outpatient level 2 through 4 visits, and their use generally will not impose new per-visit documentation requirements.

Hospital outpatient rules: There are two particularly relevant issues addressed in this final regulation. The payment rates for pulmonary rehab are:

Pulmonary Rehab via **G0424** – APC 5733, \$55.90 with co-pay of \$11.18

Pulmonary Rehab via **G0237, 38, 39** – APC 5732, \$32.12 with co-pay of \$6.43

This regulation is also the vehicle for CMS addressing issues related to Section 603/site of service payment issues. As physicians know, CMS enacted Section 603 of the 23015 Budget Act that puts notable restrictions on payment for certain hospital outpatient services provided off campus (more than 250 yards from main campus of the hospital). NAMDRRC is most concerned about the impact on pulmonary rehab – under the rules, off-campus programs that are grandfathered (“excepted” is

the CMS term) as long as they were billing for those services at that location November 2015. However, if a hospital chooses to open a new program, or relocate an existing program to a different location, the payment principles that apply are physician fee schedule rates rather than hospital outpatient rates. In the proposed rule posted this past July, CMS had proposed that even a new service provided in an excepted (grandfathered) setting would be subject to PFS payment rates rather than hospital outpatient rates. CMS has withdrawn that proposal for the coming year, so new services in excepted settings will be covered. “Excepted” is actually CMS’ terminology, which is used to refer to off-campus outpatient facilities that were offering services in November 2015. Services that do not meet that singular criterion are considered nonexcepted (not grandfathered), and those services are paid at the physician fee schedule rate.

DME: In its proposed rule this past summer, CMS actually acknowledged flaws in the structure of the competitive bidding system for DME (including oxygen, CPAP, and certain ventilators referred to by CMS as respiratory assist devices). Specifically, related to oxygen, there is also acknowledgement of reductions in liquid oxygen utilization, a story we have been pushing for years. The CMS proposed rule would have tied liquid portable payment rates to portable concentrator and transfill system payment rates, a genuine bump in actual \$\$.

More than a dozen societies joined to respond to the proposed rule, including NAMDRRC, CHEST, and ATS.

In the final rule, CMS is moving forward with its proposal, acknowledging that it will need to monitor shifts in the oxygen marketplace and adjust their payment policies accordingly.

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Congratulations, CHEST 2018 Winners

Everyone who attended CHEST Annual Meeting 2018 is a winner, but we would like to call out the winners participating in CHEST's special categories of awards and events.

ANNUAL CHEST AWARDS

- **Master FCCP**
David Gutterman, MD, Master FCCP
- **Distinguished Service Award**
David Gutterman, MD, Master FCCP
- **College Medalist Award**
Ghada Bourjeily, MD, FCCP
- **Master Clinician Educator**
Lisa Moores, MD, FCCP
- **Early Career Clinician Educator**
Amy Morris, MD, FCCP
- **Alfred Soffer Award for Editorial Excellence**
Jean Rice
- **Presidential Citation**
Darcy Marciniuk, MD, FCCP
- **Presidential Citation**
D. Robert McCaffree, MD, Master FCCP

HONOR LECTURES AND MEMORIAL AWARDS

- **Edward C. Rosenow III, MD, Master FCCP/Master Teacher Honor Lecture**
Accelerated Aging in COPD and Its Comorbidities: Novel Therapeutic Targets
Peter Barnes, MD, Master FCCP
The lecture is generously funded by the CHEST Foundation.
- **Distinguished Scientist Honor Lecture in Cardiopulmonary Physiology**
Understanding Diaphragm Performance: The Role of Ultrasound
F. Dennis McCool, MD, FCCP
The lecture is generously funded by the CHEST Foundation.
- **Presidential Honor Lecture**
Asthma: Past, Present, and Future
Jay Peters, MD, FCCP
- **Thomas L. Petty, MD, Master FCCP Memorial Lecture**
Recent Developments in Pulmonary

Rehabilitation and Long-Term Oxygen Therapy: Would Tom Petty be Pleased?

Richard Casaburi, MD, PhD, FCCP

The lecture is generously funded by the CHEST Foundation.

- **Margaret Pfrommer Memorial Lecture in Long-term Mechanical Ventilation**

Saving Lives...One Ventilator at a Time - HMV in 2018 and Beyond

Douglas McKim, MD, FCCP

The Margaret Pfrommer Memorial Lecture in Long-term Mechanical Ventilation is generously supported by International Ventilator Users Network of Post-Polio Health International and the CHEST Foundation.

- **Pasquale Ciaglia Memorial Lecture in Interventional Medicine**

Evolution of Endobronchial Ultrasound: From Diagnostics to Therapeutics

Kazuhiro Yasufuku, MD, PhD, FCCP

The lecture is generously funded by the CHEST Foundation.

- **Roger C. Bone Memorial Lecture in Critical Care**

Methylprednisolone in ARDS: A Highly Effective Treatment. How it Works, How to Use it

G. Umberto Meduri, MD

The lecture is generously funded by the CHEST Foundation.

CHEST FOUNDATION GRANT WINNERS

- **Distinguished Scholar**

Robert C. Hyzy, MD, FCCP

Eli Lilly and Company Distinguished Scholar in Critical Care Medicine

Grant Title: The Use of Electrical Impedance Tomography to Assess Mechanical Ventilation in Acute Respiratory Distress Syndrome

This grant is made possible due to the philanthropic support from Eli Lilly and Company.

- **Community Service Grantees**

Deborah Haisch, MD

Columbia University Medical Center – New York, NY

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

Grant Title: East African Training Initiative in Pulmonary and Critical Care Medicine

Pamela Garrett, CCRN, MN

Gwinnett Medical Center – Lawrenceville, GA

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

Grant Title: Breathe Better Gwinnett

Phillip Sheridan

Mobile Care Chicago – Chicago, IL

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

Grant Title: Home Environment Education for Children with Asthma

These grants are supported in full by the CHEST Foundation.

Research Grant Winners

- **Ayodeji Adegunsoye, MD, MS**

Research Grant in Pulmonary Fibrosis

Grant Title: Impact of Telomere Length on Pulmonary Fibrosis Clusters Across Diverse Racial Cohorts

- **Justin Oldham, MD, MS**

Research Grant in Pulmonary Fibrosis

Grant Title: Plasma Biomarkers to Predict Outcomes and Treatment Response in Patients with Pulmonary Fibrosis

These grants above are supported by Boehringer Ingelheim Pharmaceuticals, Inc and Genentech.

- **Jacob Brenner, MD, PhD**

Research Grant in Chronic Obstructive Pulmonary Disease

Grant Title: Ambulatory Cuirass Ventilation for Relief of Exertional Dyspnea in Severe COPD Patients

- **William Zhang, MD**

Research Grant in Chronic Obstructive Pulmonary Disease

Grant Title: Pulmonary Iron Overload as a Novel COPD Endotype

These grants above are supported by AstraZeneca LP and Sunovion Pharmaceuticals Inc.

- **Margaret Bublitz, PhD**

CHEST Foundation Research Grant in Women's Lung Health

Grant Title: Sex as a Predictor of Sleep-Disordered Breathing and Its Consequences in Pregnancy

This grant is supported in full by the CHEST Foundation.

- **Tim Morris, MD, FCCP**

CHEST Foundation Research Grant in Venous Thromboembolism

Grant Title: Long-term Follow-up of Acute Pulmonary Embolism

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- **Monica Mukherjee, MD, MPH**

CHEST Foundation Research Grant in Pulmonary Arterial Hypertension

Grant Title: Exercise Provocation in the Noninvasive Detection of Occult Right Ventricular Dysfunction and Emerging Pulmonary Hypertension in Systemic Sclerosis

This grant is supported in full by the CHEST Foundation.

- **Don Sanders, MD, MS**

CHEST Foundation Research Grant in Cystic Fibrosis

Grant Title: Whole-genome Shotgun Sequencing of Oropharyngeal Swabs in Infants With CF

This grant is supported by Vertex Pharmaceuticals.

- **Imran Sulaiman, MD, PhD**

CHEST Foundation Research Grant in Nontuberculosis Mycobacteria Diseases

Grant Title: Lower Airway Microbiota Signatures Associated With Impaired Immune Response in Non-Tuberculous Mycobacterium

This grant is supported by Insmad.

- **Samira Shojaee, MD, MPH, FCCP**

CHEST Foundation Research Grant in Lung Cancer

Grant Title: Extracellular Vesicle miRNA as a Biomarker in Malignant Pleural Effusion

This grant is supported in full by the CHEST Foundation.

- **Anna Volerman, MD**

CHEST Foundation Research Grant in Severe Asthma

Grant Title: A Randomized Clinical Trial Evaluating the Effectiveness of Virtual Teach-to-Goal(TM) Education versus Brief Intervention for Children with Severe Asthma

This grant is supported by AstraZeneca LP.

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ABSTRACT AND CASE REPORT WINNERS**• Alfred Soffer Research Award Winners**

Clauden Louis, MD: Left ventricular assist devices in Intermacs 1 acute cardiogenic shock patients

Babith J. Mankidy, MBBS, FCCP: Reduction in in-hospital cardiac arrest with early interventions in the emergency department and non-ICU units by a novel approach of rapid response teams and mobile ICU management

• Young Investigator Award Winners

Fayez Kheir, MD, MSc: Intrapleural tissue plasminogen activator and deoxyribonuclease therapy vs early medical thoracoscopy for treatment of pleural infection: a randomized clinical trial

Michael Rosman, MD: The utility of end tidal CO₂ (ETCO₂) monitoring during in-hospital cardiac arrest to predict return of spontaneous circulation

• Top 5 Abstract Poster Winners

Neha Agarwal, MD: The 3 wishes project: a feasible intervention to improve end of life care in the ICU at UCLA

Hiroaki Harada, MD: Usefulness of comprehensive preoperative pulmonary rehabilitation program including intensive nutritional support concomitant with physical exercise through an interdisciplinary team approach

Joseph M. Carrington, DO, MHA: Targeting the trans-IL-6 signaling pathway to reduce agriculture organic dust exposure-induced airway inflammation in mice

Yu Kuang Lai, MBBCh: The utility of parametric response mapping in pulmonary graft vs host disease following hematopoietic stem cell transplant

• Top Abstract Poster Finalists

Ligia M. Puiu, MD, PhD, FCCP: Association between echocardiographic and lipid parameters to workers in the metalliferous mines

Kush R. Dholakia, MD: Colloids vs crystalloids for postoperative resuscitation in patients undergoing off-pump coronary artery bypass surgery

Kulothungan Gunasekaran, MD,

MBBS: Risk of VTE in idiopathic pulmonary fibrosis: a systematic review

Laura B. Sutton, PharmD: Ease and correct use of Ellipta by age in patients with asthma and COPD

Ankur Mogla, MD: To assess the utilization of pulmonary function testing for perioperative respiratory complications in bariatric surgery patients

Ali Ammar: Tracheostomy and admission diagnosis as predictors for an extended length of stay (ELOS)

Charlene Kalani, PharmD: Efficacy and safety of direct oral anticoagulants (DOACs) in morbidly obese patients

Jonghoo Lee, MD: Performances of modified CRB-65 score compared to SIRS and QSOFA as a rapid screening tool for sepsis among infected patients in initial emergency department: a propensity score matching study

Frank J. Trudo, MD, FCCP: Clinical burden of eosinophilic COPD

Elise L. Stephenson, MD: Vitamin C and point of care glucose measurements: a retrospective, observational study

Faisal Siddiqi, MD: Implementation of an early mobility program in the medical ICU

Eileen Harder, MD: Connective tissue disease-associated pulmonary arterial hypertension hospitalizations from 2001-2014

Sophie Korzan, MD: Exhaled nitric oxide and asthma-COPD overlap in patients hospitalized with exacerbations of airway disease: preliminary observations

Andreas Grove, MD: MicroRNA (MIRNA) and biological markers discriminate between normotensive and prehypertensive young men in hypobaric hypoxic environments

Snigdha Nutalapati, MBBS: Large cell neuroendocrine cancer of the lung: SEER 2004-2014 analysis

Anubhav Jain, MBBS: Survival benefit of beta-blockers in patients hospitalized for acute exacerbation of COPD

• Case Report Slide Winners

Ze Ying Tan: All that wheezes is not asthma

Jason Lam: Pulmonary mucor mycetoma

Adam Young: Nonresolving pneu-

monia and cyclic fevers in an immunocompetent patient

Ritu Modi: Histopathological misdiagnosis of pulmonary coccidioides

Argun Can: A rare inborn error of fatty acid oxidation presenting with severe hyperammonemia in the ICU

Morgan Gilani: A colorful cause of cardiovascular collapse

Katie Jeans: A sweet surprise

Anthony Mattox: Unusual case of interstitial lung disease

Andrew Berglund: Pulmonary light chain deposition disease in a 29-year-old army soldier

Cristia Maysol Morales: A case report of a primary malignant melanoma of anterior mediastinum

Anthony McClafferty: Fibrosing mediastinitis and rheumatoid arthritis: an autoimmune inflammatory connection

Ahmed Munir: HIV with disseminated tularemia: a rare presentation

Benjamin Garren: Mycobacterium avium complex mediastinal lymphadenitis in an immunocompetent adolescent with erosion into the airway

Robert Hilton: Obtunded with a chest mass: a case of a rare neurologic paraneoplastic syndrome,

Audra Schwalk: Mucoepidermoid carcinoma: a rare malignancy treated endobronchially

Jessica Riggs: Successful transplantation defies genetics: a case of rapidly-progressive pulmonary fibrosis due to Hermansky-Pudlak syndrome

Meghan Cirulis: Acute vasodilator testing: an opportunity to refine study design and provide precision care in pulmonary hypertension

Patrick Chan: VATS lobectomy for bronchial atresia in an adult

Andrew Mehlman: Multivessel coronary artery aneurysms presenting as myocardial ischemia

Scott Maughan: Diagnosing millitary Mycobacterium bovis from the prostate of an immunocompetent host

Adam Austin: Survived ECMO, death by BLASTO: the first reported fatal case of disseminated blastomycosis in pregnancy

Tie: Donnie Carter: Subclinical polycythemia vera presenting as extensive thrombosis due to massive transfusion, *and*

Lindsay Hammons: Rare case of Serratia pneumonia causing transient aplastic anemia

Paola Baskin: Novel observations during point-of-care ultrasound (POCUS) in cardiopulmonary resuscitation: a case of ultrasound-guided probe pressure to reduce esophageal insufflation during bag-valve-mask ventilator

David Dennis: Pulmonary alveolar proteinosis presenting as intracerebral nocardiosis

Rakin Choudhury: Severe asthma caused by therapy-resistant asthmatic granulomatosis

Andrew Lytle: Lung adenocarcinoma in a patient with Turcot syndrome

Chelsea Leipold: Case of a granulomatous-lymphocytic interstitial lung disease in a patient with common variable immunodeficiency disorder

Galyna Ivashchuk: Double trouble: ANCA vasculitis with concomitant IGA nephropathy presenting as massive diffuse alveolar hemorrhage and fulminant renal failure

• Case Report Poster Winners

Christine Zhou: Role of transbronchial lung cryobiopsy in the diagnosis of adenocarcinoma in situ

Parin Shah: A rare case of Erdheim-Chester disease masquerading as metastatic lung cancer

Avanthika Wynn : A rare asthma mimic

Muhammad S. Ali: Severe pancolitis: a rare adverse effect of nintedanib

Brian Foster: Don't forget to breathe: a case of hypoxemia after carotid body resection

Kelly Pennington: Intra-cardiac embolization of an inferior vena cava filter resulting in cardiac arrest

George Elkomos-Botros: Acute generalized exanthematous pustulosis presenting as distributive shock with multi-organ failure

Ashley M. Scott: Avian occupational hypersensitivity pneumonitis in a restaurant employee

Andrew Polito: Pulmonary amyloidosis: an unusual presentation of a rare disease

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Introducing CHEST's new CEO/EVP

Greetings! My name is Robert Musacchio; I am proud to introduce myself as the new Chief Executive Officer and Executive Vice President of CHEST. I am honored to join this team of distinguished clinicians as we spearhead progress in the fight against lung disease.

I have had the pleasure of working at CHEST for the last 4 years, first joining CHEST Enterprises as Senior Vice President of Business Development. In that role, I focused on revenue growth and product diversification before becoming COO of CHEST. As COO, I dedicated myself to strengthening our team by mentoring staff and collaborating with senior leadership, a challenge that I have deeply enjoyed.

Before joining CHEST, I worked at the American Medical Association for 35 years in roles encompassing research, advocacy, membership, and publishing. I also worked with boards and membership groups as a member of the AMA's CPT® Editorial Panel and as a publisher for *JAMA*.

As CEO, I hope to leverage those experiences to support CHEST in its mission, which is to improve lung health not just for 1 year but for the next 25 years. For that reason, our leadership team has outlined an organizational culture that fosters short-term success and long-term innovation, focusing on four key areas:

People: How do we attract and retain the right people?

Strategy: How do we create a truly differentiated strategy?

Execution: How do we improve our process to drive flawless execution?

Resources: How do we ensure that we have sufficient resources to invest in our mission?

Those questions in mind, we have established several standards that guide the way we work. We are focusing on leading with integrity, cultivating passion and innovation, honoring our team, and having fun while we deliver cutting-edge education and create community for our members. With these norms, we can continue to foster an environment that generates results. This, in turn, will enable CHEST to fulfill its core purpose of crushing lung disease.

We can crush lung disease by arming our members with industry-leading education offerings—including simulation experiences and live lab courses—and expanding them worldwide to Thailand and Greece in 2019. We can crush lung disease by using cutting-edge technologies—including interactive gaming platforms—to glean further insights. We can crush lung disease by connecting our membership of nearly 20,000 pulmonary, critical care, and sleep medicine professionals to innovative education tools, along with a network of prestigious colleagues to deliver the



Robert Musacchio

highest quality patient care.

Most importantly, we can crush lung disease by empowering our members in their work—if you care about lung disease, we care about you!

If you care about lung disease, I am excited to partner with you in this cause. I am thankful for this opportunity to lead CHEST and the CHEST Foundation into the future and look forward to working with you.



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CRITICAL CARE COMMENTARY

The 1-hour sepsis bundle is serious—serious like a heart attack

BY AMIT UPPAL, MD

In 2002, the European Society of Intensive Care Medicine, the Society of Critical Care Medicine, and the International Sepsis Forum formed the Surviving Sepsis Campaign (SSC) aiming to reduce sepsis-related mortality by 25% within 5 years, mimicking the progress made in the management of STEMI (<http://www.survivingsepsis.org/About-SSC/Pages/History.aspx>).

SSC bundles: a historic perspective

The first guidelines were published in 2004. Recognizing that guidelines may not influence bedside practice



Dr. Amit Uppal

for many years, the SSC partnered with the Institute for Healthcare Improvement to apply performance improvement methodology to sepsis management, developing the “sepsis change bundles.” In addition to hospital resources for education, screening, and data collection, the 6-hour resuscitation and 24-hour management bundles were created. Subsequent data, collected as part of the initiative, demonstrated an association between bundle

compliance and survival.

In 2008, the SSC guidelines were revised, and the National Quality Forum (NQF) adopted sepsis bundle compliance as a quality measure. NQF endorsement is often the first step toward the creation of mandates by the Centers for Medicare and Medicaid Services (CMS), but that did not occur at the time.

In 2012, the SSC guidelines were updated and published with new 3- and 6-hour bundles. That year, Rory Staunton, an otherwise healthy 12-year-old boy, died of septic shock in New York. The public discussion of this case, among other factors, prompted New York state to develop a sepsis care mandate that became state law in 2014. An annual public report details each hospital’s compliance with process measures and risk-adjusted mortality. The correlation between measure compliance and survival also holds true in this data set.

In 2015, CMS developed the SEP-1 measure. While the symbolic importance of a sepsis federal mandate and its potential to improve patient outcomes is recognized, concerns remain about the measure itself. The detailed and specific way data must be collected may disconnect clinical care provided from measured compliance. The time pressure and the “all-or-nothing” approach might incentivize interventions potentially harmful in some patients. No patient-centered outcomes are reported. This measure might be tied to reimbursement in the future.

The original version of SEP-1 was based on the 2012 SSC bundles, which reflected the best evidence available at the time (the 2001 Early Goal-Directed Therapy trial). By 2015, elements of that strategy had been challenged, and the PROCESS, PROMISE, and ARISE trials contested the notion that protocolized resuscitation decreased mortality. Moreover, new definitions of sepsis syndromes (Sepsis-3) were published in 2016 (Singer M, et al. *JAMA*. 2016;315[8]:801).

The 2016 SSC guidelines adopted the new definitions and recommended that patients with sepsis-induced hypoperfusion immediately receive a 30 mL/kg crystalloid bolus, followed by frequent reassessment.

CMS did not adopt the Sepsis-3 definitions, but updates were made to allow the clinicians flexibility to demonstrate reassessment of the patient.

Comparing the 1-hour bundle to STEMI care

This year, the SSC published a 1-hour bundle to replace the 3- and 6-hour bundles (Levy MM et al. *Crit Care Med*. 2018;46[6]:997). Whereas previous bundles set time frames for completion of the ele-

ments, the 1-hour bundle focuses on the initiation of these components. The authors revisited the parallel between early management of sepsis and STEMI. The 1-hour bundle includes serum lactate, blood cultures prior to antibiotics, broad-spectrum antibiotics, a 30 mL/kg crystalloid bolus for patients with hypotension or lactate value greater than or equal to 4 mmol/L, and vasopressors for persistent hypotension.

not for public reporting, former bundles have been adopted as federally regulated measures. Has the SSC gone too far? Are these concerns enough to abandon the 1-hour bundle? Or are the concerns regarding the 1-hour bundle an example of “perfect is the enemy of better”? To understand the potential for imperfect guidelines to drive tremendous patient-level improvements, one must consider the evolution of STEMI management.

Consider the complexity of getting a patient from their home to a catheterization lab within 90 minutes, even in ideal circumstances. This short time frame encourages, by design, a low threshold to activate the system.

Elements of controversy after the publication of this bundle include:

1 One hour seems insufficient for complex clinical decision making and interventions for a syndrome with no specific diagnostic test: sepsis often mimics, or is mimicked by, other conditions.

2 Some bundle elements are not supported by high-quality evidence. No controlled studies exist regarding the appropriate volume of initial fluids or the impact of timing of antibiotics on outcomes.

3 The 1-hour time frame will encourage empiric delivery of fluids and antibiotics to patients who are not septic, potentially leading to harm.

4 While the 1-hour bundle is a quality improvement tool and

Since the 1970s, the in-hospital mortality for STEMI has decreased from 25% to around 5%. The most significant factor in this achievement was the recognition that early reperfusion improves outcomes and that doing it consistently requires complex coordination. In 2004, a Door-to-Balloon (D2B) time of less than 90 minutes was included as a guideline recommendation (Antman EM, et al. *Circulation*. 2004;110[5]:588). CMS started collecting performance data on this metric, made that data public, and later tied the performance to hospital reimbursement.

Initially, the 90-minute goal was achieved in only 44% of cases. In 2006, the D2B initiative was launched, providing recommendations for public education, coordination of care, and emergent management of STEMI. Compliance with these recommendations required significant education and changes to STEMI care at multiple levels. Data were collected and submitted to inform the process. Six years later, compliance with the D2B goal had increased from 44% to 91%. The median D2B dropped from 96 to 64 minutes. Based on high compliance, CMS discontinued the use of this metric for reimbursement as the variation between high and low performers was minimal. Put simply, the entire country had

The Society of Critical Care Medicine partnered with the Institute for Healthcare Improvement to apply performance improvement methodology to sepsis management.

gotten better at treating STEMI. The “time-zero” for STEMI was pushed back further, and D2B has been replaced with first-medical-contact (FMC) to device time. The recommendation is to achieve this as quickly as possible, and in less than 90 minutes (O’Gara P, et al. *JACC*. 2013;61[4]:485).

Consider the complexity of getting a patient from their home to a catheterization lab within 90 minutes, even in ideal circumstances. This short time frame encourages, by design, a low threshold to activate the system. We accept that some patients will receive an unnecessary catheterization or systemic fibrinolysis although the recommendation is based on level B evidence.

Compliance with the STEMI guidelines is more labor-intensive and complex than compliance with the 1-hour sepsis bundle. So, is STEMI a fair comparison to sepsis? Both syndromes are common, potentially deadly, and time-sensitive. Both require early recognition, but

neither has a definitive diagnostic test. Instead, diagnosis requires an integration of multiple complex clinical factors. Both are backed by imperfect science that continues to evolve. Over-diagnosis of either will expose the patient to potentially harmful therapies.

The early management of STEMI is a valid comparison to the early management of sepsis. We must consider this comparison as we ponder the 1-hour sepsis bundle.

Is triage time the appropriate time-zero? In either condition, triage time is too early in some cases and too late in others. Unfortunately, there is no better alternative, and STEMI guidelines have evolved to start the clock before triage. Using a point such as “recognition of sepsis” would fail to capture delayed recognition.

Is it possible to diagnose and initiate treatment for sepsis in such a short time frame? Consider the treatment received by the usual care group of the PROCESS trial (The ProCESS Investigators. *N*

Engl J Med. 2014;370:1683). Prior to meeting entry criteria, which occurred in less than 1 hour, patients in this group received an initial fluid bolus and had a lactate assessment. Prior to randomization, which occurred at around 90 minutes, this group completed 28 mL/kg of crystalloid fluid, and 76% received antibiotics. Thus, the usual-care group in this study nearly achieved the 1-hour bundle currently being contested.

Is it appropriate for a guideline to strongly recommend interventions not backed by level A evidence? The recommendation for FMC to catheterization within 90 minutes has not been studied in a controlled way. The precise dosing and timing of fibrinolysis is also not based on controlled data. Reperfusion devices and antiplatelet agents continue to be rigorously studied, sometimes with conflicting results.

Finally, should the 1-hour bundle be abandoned out of concern that it will be used as a national

performance metric? First, there is currently no indication that the 1-hour bundle will be adopted as a performance metric. For the sake of argument, let’s assume the 1-hour bundle will be regulated and used to compare hospitals. Is there reason to think this bundle favors some hospitals over others and will lead to an unfair comparison? Is there significant inequity in the ability to draw blood cultures, send a lactate, start IV fluids, and initiate antibiotics?

Certainly, national compliance with such a metric would be very low at first. Therein lies the actual problem: a person who suffers a STEMI anywhere in the country is very likely to receive high-quality care. Currently, the same cannot be said about a patient with sepsis. Perhaps that should be the focus of our concern.

Dr. Uppal is Assistant Professor, NYU School of Medicine, Bellevue Hospital Center, New York, New York.



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PULMONARY PERSPECTIVES®

Use of ECMO in the management of influenza-associated ARDS

BY GENEVA TATUM, MD, FCCP

Now that we are in the midst of flu season, many discussions regarding the management of patients with influenza virus infections are ensuing. While prevention is always preferable, and we encourage everyone to get vaccinated, influenza remains a rapidly widespread infection. In the United States during last year's flu season (2017-18), there was an estimated 49 million cases of influenza, 960,000 hospitalizations, and 79,000 deaths. Approximately 86% of all deaths were estimated to occur in those aged 65 and older (Centers for Disease Control and Prevention webpage on Burden of Influenza <https://www.cdc.gov/flu/about/burden/estimates.htm#table1>).

Despite our best efforts, there are inevitable times when some patients become ill enough to require hospitalization. Patients aged 65 and

older make up the overwhelming majority of patients with influenza who eventually require hospitalization (Fig 1) (The Centers for Disease Control and Prevention Flu-View Database. <https://gis.cdc.gov/grasp/fluview/FluHospChars.html>). Comorbidities also confer higher risk for more severe illness and potential hospitalization irrespective of age (Fig 2). In children with known medical conditions, asthma confers highest risk of hospitalization, as 27% of those with asthma were hospitalized after developing the flu. In adults, 52% of those with cardiovascular disease and 30% of adult patients with chronic lung disease who were confirmed to have influenza required hospitalization for treatment (Fig 2, The Centers for Disease Control and Prevention Flu-View Database. <https://gis.cdc.gov/grasp/fluview/FluHospChars.html>).

The most severe cases of influenza can require ICU care and advanced



DR. TATUM

management of respiratory failure as a result of the acute respiratory distress syndrome (ARDS). The lungs suffer significant injury due to the viral infection, and they lose their ability to effectively oxygenate the blood. Secondary bacterial infections can also occur as a complication, which compounds the injury. Given the fact that so many patients have significant comorbidities and are of advanced age, it is reasonable

recover from acute injury. Venovenous (VV) ECMO requires peripheral insertion of large cannulae into the venous system to take deoxygenated blood, deliver it through the membrane oxygenator, and return the oxygenated blood back to the venous system. In simplest terms, the membrane of ECMO circuit serves as a substitute for the gas exchange function of the lungs and provides the oxygenation that the injured alveoli of the lung are unable to provide. The overall intent is to have the external ECMO circuit do all of the gas exchange work while the lungs heal.

Much research has been done on VV ECMO as an adjunct or salvage therapy in patients with refractory hypoxemic respiratory failure due to ARDS. Historical and recent studies have shown that approximately 60% of patients with ARDS have viral (approximately 20%) or bacterial (approximately 40%) pneumonia as the underlying cause (Zapol, et al. *JAMA*. 1979; 242[20]:2193; Combes A, et al. *N Engl J Med*. 2018;378:1965). Naturally, given the frequency of infection as a cause for ARDS, and the severity of illness that can develop with influenza infection in particular, an interest has

The membrane of ECMO circuit serves as a substitute for the gas exchange function of the lungs and provides the oxygenation that the injured alveoli of the lung are unable to provide. The overall intent is to have the external ECMO circuit do all of the gas exchange work while the lungs heal.

to expect that a fair proportion of those with influenza would develop respiratory failure as a consequence. For some of these patients, the hypoxemia that develops as a result of the lung injury can be exceptionally challenging to manage. In extreme cases, conventional ventilator management is insufficient, and the need for additional, advanced therapies arise.

Studies of VV ECMO in severe influenza

ECMO (extracorporeal membrane oxygenation) is a treatment that has been employed to help support patients with severe hypoxemic respiratory failure while their lungs

arisen in the applicability of ECMO in cases of severe influenza-related ARDS.

In 2009, during the H1N1 influenza pandemic, the ANZ ECMO investigators in Australia and New Zealand described a 78% survival rate for their patients with severe H1N1-associated ARDS treated with VV ECMO between June and August of that year (Davies A, et al. *JAMA*. 2009;302[17]:1888). The eagerly awaited results of the randomized, controlled CESAR trial (Peek G, et al. *Lancet*. 2009;374:1351) that studied patients aged 18 to 64 with severe, refractory respiratory failure transferred to a specialized center for ECMO care had addition-



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al impact in catalyzing interest in ECMO use. This trial showed improved survival with ECMO (63% in ECMO vs 47% control, RR 0.69; 95% CI 0.05-0.97 $P=0.03$) with a gain of 0.03 QALY (quality-adjusted life years) with additional cost of 40,000 pounds sterling. However, a major critique is that 24% of patients transferred to the specialized center never were treated with ECMO. Significantly, there was incomplete follow-up data on nearly half of the patients, as well. Many conclude that the survival benefit seen in this study may be more reflective of the expertise in respiratory failure management (especially as it relates to lung protective ventilation) at this center than therapy with ECMO itself.

Additional cohort studies in the United Kingdom (Noah MA, et al. *JAMA*. 2011;306[15]:1659) and Italy (Pappalardo F, et al. *Intensive Care Med*. 2013;39[2]:275) showed approximately 70% in-hospital survival rates for patients with H1N1 influenza transferred to a specialized ECMO center and treated with ECMO.

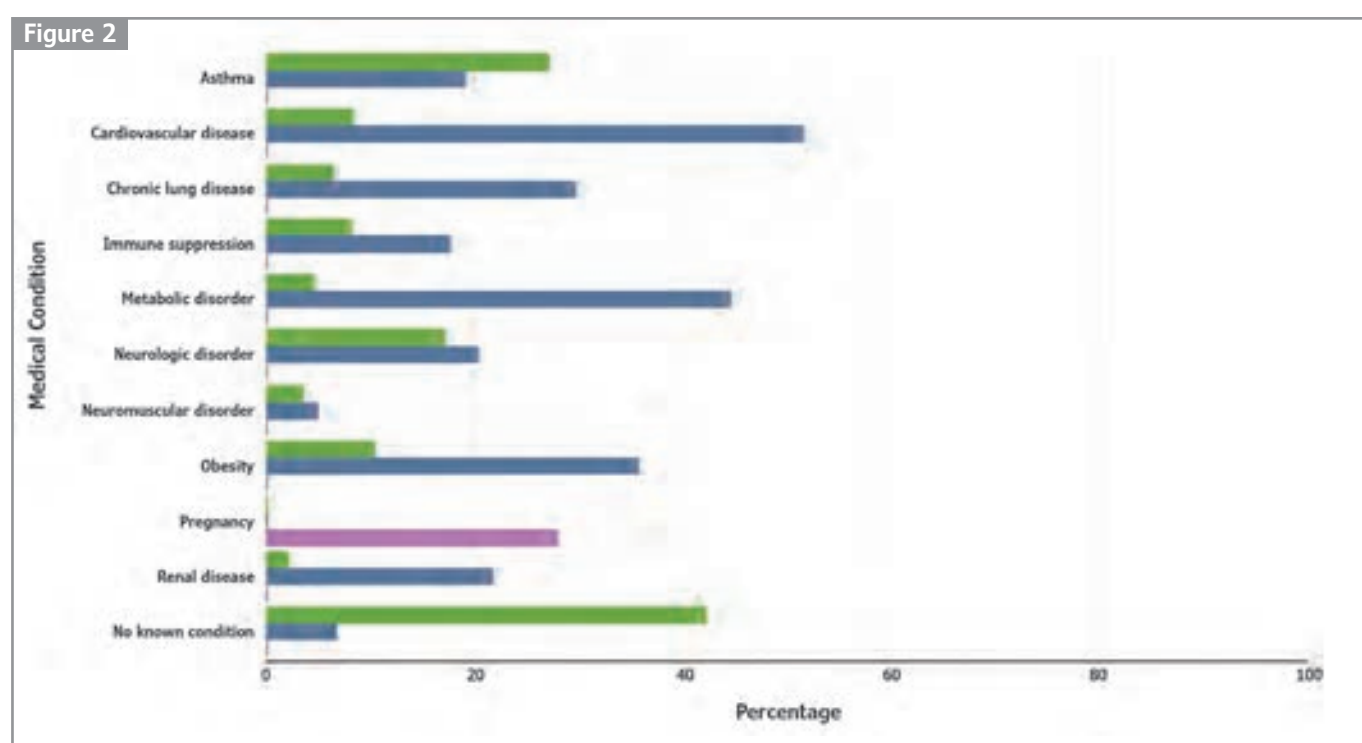
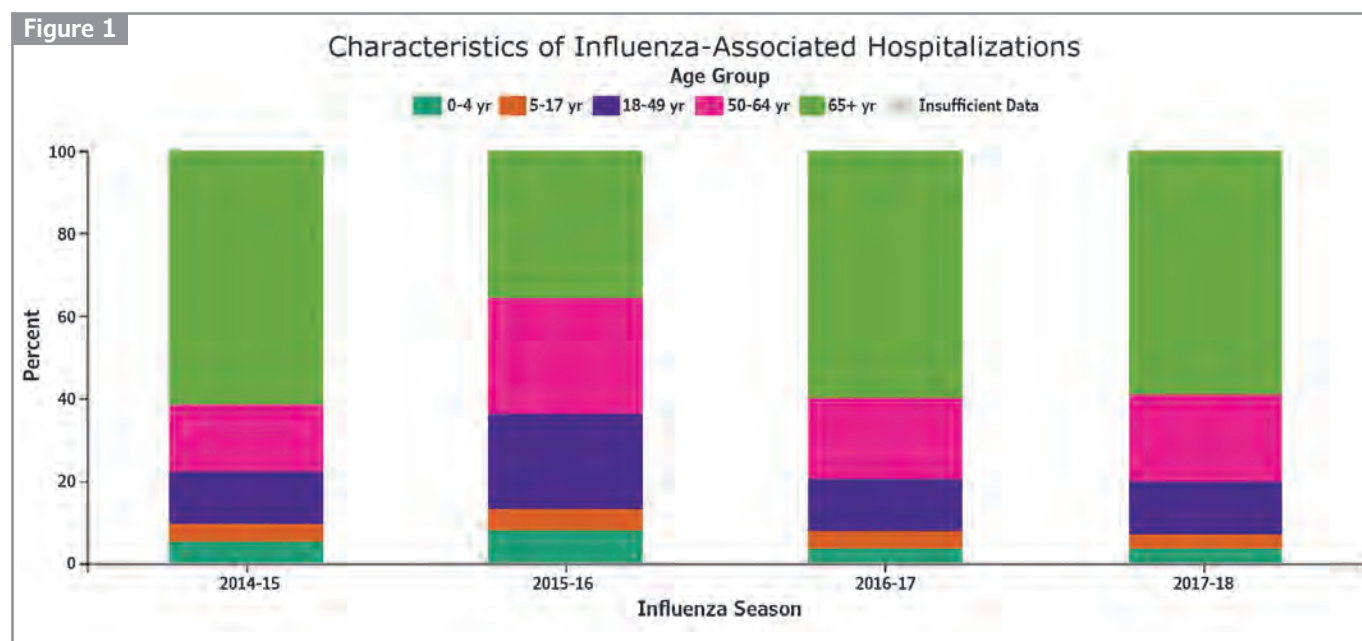
Nonetheless, the information gained from the observational data from ANZ ECMO, along with data published in European cohort studies and the randomized controlled CESAR trial after the 2009 H1N1 influenza pandemic, greatly contributed to the rise in use of ECMO for refractory ARDS due to influenza. Subsequently, there has been a rapid establishment and expansion of ECMO centers over the past decade, primarily to meet the anticipated demands of treating severe influenza-related ARDS.

The recently published EOLIA trial (Combes A, et al. *N Engl J Med*. 2018;378:1965) was designed to study the benefit of VV ECMO vs conventional mechanical ventilation

CMS recently released new DRG reimbursement scales for the use of ECMO effective Oct 1, 2018. VV ECMO could have as much as a 70% reduction in reimbursement, and many insurance companies are expected to follow suit.

in ARDS and demonstrated an 11% absolute reduction in 60-day mortality, which did not reach statistical significance. Like the CESAR trial, there are critiques of the outcome, especially as it relates to stopping the trial early due to the inability to show a significant benefit of VV ECMO over mechanical ventilation.

All of the aforementioned stud-



ies evaluated adults under age 65. Interestingly, there are no specific age contraindications for the use of ECMO (ELSO Guidelines for Cardiopulmonary Extracorporeal Life Support, Extracorporeal Life

outcome benefit of ECMO for a relatively healthy patient over age 65 is not known, as those patients have not been evaluated in studies thus far. When comparison to data from decades ago is made, one must keep in mind that populations worldwide are living longer, and a continued increase in number of adults over the age 65 is expected.

While the overall interpretation of the outcomes of studies of ECMO may be fraught with controversy, there is little debate that providing care for patients with refractory respiratory failure in centers that provide high-level skill and expertise in management of respiratory failure has a clear benefit, irrespective of whether the patient eventually receives therapy with ECMO. What is also clear is that ECMO is costly, with per-patient costs demonstrated to be at least double that of those receiving mechanical venti-

lation alone (Peek G, et al. *Lancet*. 2009;374:1351). This substantial cost associated with ECMO cannot be ignored in today's era of value-based care.

Fortuitously, CMS recently released new DRG reimbursement scales for the use of ECMO effective Oct 1, 2018. VV ECMO could have as much as a 70% reduction in reimbursement, and many insurance companies are expected to follow suit (CMS Changes in ECMO Reimbursements – ELSO Report. <https://www.else.org>). Only time will tell what impact this, along with the current evidence, will have on long-term provision of ECMO care for our sickest of patients with influenza and associated respiratory illnesses.

Dr. Tatem is with the Division of Pulmonary and Critical Care Medicine, Department of Medicine, Henry Ford Hospital, Detroit, Michigan.

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By Dr. E. Henkle, et al.

Persistence of Central Venous Oxygen Desaturation During Early Sepsis Is Associated With Higher

Mortality: A Retrospective Analysis of the ALBIOS Trial.

By Dr. A. Protti, et al.

Predictors of Asthma/COPD Overlap in FDNY Firefighters With World Trade Center Dust Exposure: A Longitudinal Study.

By Dr. A. Singh, et al.

Characteristics and Outcomes of Small Cell Lung Cancer Detected by CT Screening.

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FRONTLINE
MEDICAL COMMUNICATIONS

News from the CHEST Board of Regents

BY STEVEN Q. SIMPSON, MD, FCCP

In 2013, CHEST began work with the Chinese Ministry of Health and the Chinese Medical Doctor Association to establish the specialty of Pulmonary and Critical Care Medicine in China. CHEST members, among them Drs. Renli Qiao, Jack Buckley, Darcy Marciniuk, Mark Rosen, and Stephanie Levine, helped to establish a curriculum and a board exam and have now seen the first class of fellows complete their training. At our October Board meeting, Dr. Buckley reported at this meeting that the Chinese PCCM program, the first medical subspecialty to be established in China, is prepared to stand on its own, without further support from CHEST. This is a huge accomplishment for both the Chinese Medical Doctor Association and for CHEST, and the Board heartily congratulated everyone who contributed to this impressive project.

Another important function at this October meeting is to approve the Governance Committee's recommendations for a new slate of board members and a new President-Designate. The board bid farewell to four valued members at the end of their terms: Drs. Robert Aranson (Freeport, ME), Subhakar Kandi (Hyderabad, India), Janet Maurer (Desert Hills, AZ), and Hassan Bencheqroun (San Diego, CA). All contributed immensely to the success of CHEST, and the remaining board members expressed their gratitude. The Board also approved Drs. Vera De Palo (Providence, RI), Neil Freedman (Evanston, IL), Francesco DeBlasio (Napoli, Italy), and Lynn Tanoue (New Haven, CT) as at-large regents, and Dr. Steven Simpson (Kansas City, KS) as the new President-Designate. The Board is committed to ensuring that its makeup be representative of the entirety of our membership base. As CHEST continues to grow internationally and as we gain more members who are women and historically underrepresented minorities, we are dedicated to ensuring that there is no glass ceiling in our organization and that all have the opportunity to contribute to the full extent of their ability. We are, likewise, dedicated to providing mentorship and leadership opportunities for members of groups who are under-represented.

Following the resignation of CHEST's CEO during the summer, the Chief Operating Officer, Dr. Robert Musacchio, became interim CEO (see p. 65 in this issue). Dr. Musacchio is a PhD economist who joined CHEST in 2015 after a 35-year stint at the American Medical Association and who has broad and deep experience in the business of running a nonprofit medical organization. He brings an extraordinary skill set in both business and staff development to the role, and we very much look forward to working with him in this new position! Dr. Musacchio gave an update on educational efforts, domestic and international growth in membership, changes in the structure of the professional staff, and the state of our flagship journal, CHEST®.

CHEST Foundation support for young career clinicians

As the CHEST Foundation continues to grow, so does our ability to impact the careers of early career clinicians. What began as a small travel grants program for the 2015 winners of the NetWorks Challenge to help offset their trainee members' travel to CHEST 2015 in Montreal, was quickly identified as opportunity for the CHEST Foundation to deepen their engagement with early career clinicians. The CHEST Foundation travel grants program has grown immensely since then, but the core tenants of the program remain unchanged – to provide excellent trainees, medical students, and all other members of the care team with the fiscal support they need to become successful clinicians and faith-



fully treat their patients and community. Some of the ways our travel grants are put to good use is to attend the CHEST Annual Meeting and to further engage early career clinicians as active members of CHEST. In addition to travel grant support to offset the costs of attending the annual meeting, recipients of these competitive grants receive free registration to the meeting; individualized mentorship from a CHEST member who is currently or has been part of CHEST leadership (ie, served on one of the boards, as faculty, on committees, as well as chairs and vice-chairs of the NetWorks); learn best practices for applying for research and community service grants from previous grant winners; invitations to exclusive receptions to network with peers and potential employers; and access to several sessions at the annual meeting intended to strengthen their clinical skill set. All of these programmatic pieces come together to help propel these young leaders' careers and invest in the future of our discipline as CHEST clinicians.

Due to your overwhelming philanthropic support, CHEST Foundation's travel grant programs continue to flourish. In 2017, the CHEST Foundation supported a total of 43 early career clinicians' travel to attend the CHEST Annual Meeting in Toronto. Through continued donor support, a successful NetWorks Challenge fundraiser, and an overwhelming number of qualified early career applicants for the travel grants, that number swelled to 72 clinicians for the 2018 CHEST Annual Meeting in San Antonio. In total, the CHEST Foundation dispensed over \$70,000 in travel grants for CHEST 2018. We can't thank you enough for the impact you have made in these early career clinicians' professional lives, and we urge you to increase your gifts, so we can advance these important professional

development opportunities for clinicians by CHEST 2019!

"I'm so thankful to be a recipient of the CHEST travel grant! It enabled me to connect with such a wide array of health-care professionals and learn from my peers. It was wonderful to discover that there are many ways for me as a respiratory therapist to become involved in CHEST! Thank you to all the donors who made these awards a reality!"

- Maya Jenkins, RRT

"As an international medical graduate fellow, I experience challenges spanning from economic (inability to moonlight), and professional (scarce funding and sponsorship opportunities, mentorship) to immigration-related difficulties. The CHEST Foundation grant is a superbly structured and implemented opportunity that allowed me a chance to address most of these challenges as I advance in my academic career. The grant itinerary permitted me to network with mentors and, subsequently, resulted in critical leads: A collaborative research project, offers to write letters in support of my visa situation, interest from a journal for one my manuscripts, plans to submit proposals for #CHEST2019, and, most importantly, support from leaders in our field who offered guidance and sponsorship (huge shout out to Dr. Chris Carroll)! I would like to thank the Foundation for awarding this grant as it isn't just the grant but the slew of opportunities that came along with it that can, and, in my case, catapult fledgling careers in the field of pulmonary and critical care medicine."

- Viren Kaul, MD

"CHEST education is the cornerstone of pulmonary medicine and delivering world-class health care. CHEST and the CHEST Foundation care about me and the importance of being the best practitioner I can be for my patients. Having impactful conversations with other clinicians, seeing new innovations, and learning through a diverse number of ways while at CHEST 2018 gave me meaningful lessons to apply in my daily practice. The travel grant made this possible!"

- Sarah Brundidge, MSc, RRT



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FDA CLEARED INDICATIONS: The EkoSonic® Endovascular System is indicated for the ultrasound-facilitated, controlled, and selective infusion of physician-specified fluids, including thrombolytics, into the vasculature for the treatment of pulmonary embolism; the controlled and selective infusion of physician-specified fluids, including thrombolytics, into the peripheral vasculature; and the infusion of solutions into the pulmonary arteries. Instructions for use, including warnings, precautions, potential complications, and contraindications, can be found at www.ekoscorp.com. Caution: Federal (USA) law restricts these devices to sale by or on the order of a physician. **THE CE MARK (CE0086) HAS BEEN AFFIXED TO THE EKOSONIC® PRODUCT WITH THE FOLLOWING INDICATIONS:** Peripheral Vasculature: The EkoSonic® Endovascular Device, consisting of the Intelligent Drug Delivery Catheter (IDDC) and the MicroSonic™ Device (MSD), is intended for controlled and selective infusion of physician-specified fluids, including thrombolytics, into the peripheral vasculature. All therapeutic agents utilized with the EkoSonic® Endovascular System should be fully prepared and used according to the instruction for use of the specific therapeutic agent. Pulmonary Embolism: The EKOS EkoSonic® Endovascular System is intended for the treatment of pulmonary embolism patients with ≥ 50% clot burden in one or both main pulmonary arteries or lobar pulmonary arteries, and evidence of right heart dysfunction based on right heart pressures (mean pulmonary artery pressure ≥ 25mmHg) or echocardiographic evaluation.



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