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In 2018, wildfire smoke led to 24 days of poor air quality in Seattle, including 9 days rated as “unhealthy” on the U.S. Air Quality Index.

Wildfire smoke linked to COPD, asthma exacerbations, but long-term effects still under study

BY DOUG BRUNK

MDedge News

The 2019 wildfire season is underway in many locales across the United States, exposing millions of individuals to smoky conditions that will have health consequences ranging from stinging eyes to scratchy throats to a trip to the ED for asthma or chronic obstructive pulmonary disease (COPD) exacerbation. Questions about long-term health impacts are on the minds of many, including physicians and their patients who live with cardiorespiratory conditions.

John R. Balmes, MD, a pulmonologist at the University of California, San Francisco, and an expert on the respiratory and cardiovascular effects of air pollutants, suggested that the best available published literature points to “pretty strong evidence for acute effects of wildfire smoke on respiratory health, meaning people with preexisting asthma and COPD are at risk for exacerbations, and probably for respiratory tract infections as well.” He said, “It’s a little less clear, but there’s good biological plausibility for increased risk of respiratory tract infections because when your alveolar macrophages are

Wildfire smoke // continued on page 7

FDA advisory panel recommends approval of peanut desensitization therapy

BY MICHELE G. SULLIVAN

MDedge News

A pill designed to desensitize peanut-allergic children and teenagers may be on the way. The Food and Drug Administration’s Allergenic Products Advisory Committee has voted to recommend approval of the AR101 peanut protein capsules (Palforzia) for use in oral immunotherapy in those aged 4-17 years old with a confirmed peanut allergy. Conditions for approval include stipulations that a black-box warning and medication use guide are included in the packaging, the panel said. The FDA usually follows the recommendations of its advisory panels. The peanut pill is on the way.

The committee members voted 7-2 that the drug was effective and 8-1 that it was safe.

John Kelso, MD, the sole dissenter on safety, voiced concerns about the dearth of long-term follow-up in Aimmune Therapeutic’s body of research and the finding that children who received the treatment during the dose-escalation and

Peanut // continued on page 4

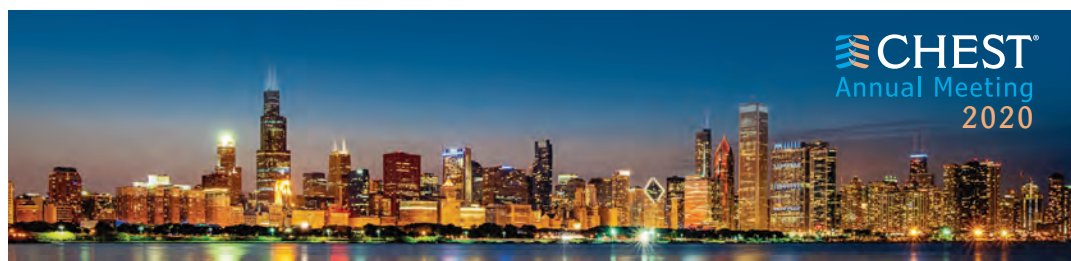
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High cost of peanut desensitization therapy remains a concern // *continued from page 1*

maintenance periods had twice the number of allergic reactions requiring epinephrine, compared with those who received placebo. There are no long-term safety data to rely on yet, he added.

“Efficacy has not been demon-

strated, except on the day the peanut challenge is administered,” said Dr. Kelso, an allergist at the Scripps Clinic, San Diego, adding that only long-term follow-up data would fully convince him that the drug’s benefits outweigh the risks.

In the discussion, however, other committee members pointed out that new drugs are often approved without long-term efficacy and safety data. Those data are extrapolated from clinical trials, and only real-world experience will confirm

the data, the investigators noted.

Company representatives did not explicitly address the potential cost of the therapy, but a recent review by the Institute for Clinical and Economic Review estimated the cost to be \$4,200 a year. Palforzia would

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have to be taken every day, for an unknown amount of time, to maintain peanut tolerance.

“Using prices from analysts for AR101 (\$4,200 a year), we estimated that only 41% of eligible patients could be treated in a given year without exceeding ICER’s budget impact threshold,” the institute concluded in

a publicly released analysis.

Palforzia comes in individual packs of capsules filled with peanut protein, not flour. The capsules come in doses of 0.5, 1, 10, 20, 100, and 300 mg. A single-dose sachet contains 300 mg. Treatment begins with 0.5-6 mg over 1 day and escalates every 2 weeks until 300 mg is

reached or there is a reaction requiring epinephrine. Passing at least a 300-mg dose was the requirement for exiting the escalation phase and moving on to the daily, year-long maintenance phase.

The four efficacy studies presented showed that 96% of patients tolerated 300 mg; 84% tolerated 600

mg; and 63% 1,000 mg – about 10 times the reactive dose observed in the placebo controls.

The capsule, however, is not a panacea. The company advises that families continue with the peanut avoidance diet. “It’s important to remember that reactive episodes can occur with dosing, and accidental exposures can occur at unpredictable times, away from home, and despite the best efforts at avoidance,” Dr. Adelman said. “This is not a drug for everyone, but it is an effective desensitization tool and would clearly be the first therapy to treat a food allergy, providing statistically significant and clinically important improvement. Outcomes align with patients’ goals.”

Safety was assessed in 709 treated patients who received the medication and 292 who received placebo. Treatment-related adverse events were most common in initial dosing: 89% of the treatment group and 58% of the placebo group experienced at least one adverse event during that time. Adverse events were mostly mild to moderate and decreased in severity over the study period.

Respiratory events were more common in those in the active group, especially in children with asthma. These events included cough, wheezing, dyspnea, dysphonia, throat irritation and tightness, and exercise-induced asthma. There was, however, no “concerning change” in asthma control.

Systemic allergic reactions and anaphylaxis were more common in the active-dose group. Systemic reactions during dose escalation occurred in 9.4% of active patients and 3.8% those taking placebo. During the maintenance phase, they occurred in 8.7% and 1.7% of patients, respectively. Three patients in the active group had a serious systemic reaction – two during up-dosing and one during maintenance. During initial dose escalation and up-dosing combined, 6.1% of patients in the active group and 3.1% in the placebo group had a systemic reaction requiring epinephrine. This was most often administered outside of the clinic.

There were 12 cases of eosinophilic esophagitis, all of which resolved after medication withdrawal from the study medication. The patch is designed to desensitize allergic children aged 4-11 years through a skin-patch method known as epicutaneous immunotherapy. Results from two controlled clinical trials were included in the submission.

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ABIM: Self-paced MOC pathway currently under development

BY ALICIA GALLEGOS

MDedge News

Physician groups are praising a new option by the American Board of Internal Medicine (ABIM) that will offer doctors a self-paced pathway for maintenance of certification (MOC) in place of the traditional long-form assessment route.

The new longitudinal assessment option, announced in late August, would enable physicians to acquire and demonstrate ongoing knowledge through shorter evaluations of specific content. The option, currently under development, also would provide doctors with immediate feedback about their answers and share links to educational material to address knowledge gaps, according to an announcement. While details are still being flushed out, a summary of the longitudinal assessment concept by the American Board of Medical Specialties explains that the approach draws on the principles of adult learning and modern technology “to promote learning, retention, and transfer of information.”

Developing a longitudinal assessment option is part of ABIM’s ongoing evolution, Marianne M. Green, MD, chair for ABIM’s board of directors and ABIM President Richard J. Baron, MD, wrote in a joint letter to internists posted on ABIM’s blog.

“We recognize that some physicians may prefer a more continuous process that easily integrates into their lives and allows them to engage seamlessly at their preferred pace, while being able to access the resources they use in practice,” the doctors wrote.

Douglas DeLong, MD, chair of the American College of Physician’s (ACP) board of regents said the option is a positive, first step that will support lifelong learning. He noted the new option is in line with recommendations by the American Board of Medical Specialties’ Continuing Board Certification: Vision for the Future Commission, which included ACP concerns.

“It’s pretty clear that some of the principles of adult learning – frequent information with quick feed-

back, repetition of material, and identifying gaps in knowledge – is really how people most effectively learn,” Dr. DeLong said in an interview. “Just cramming for an examination every decade hasn’t ever really been shown to affect long-term retention of knowledge or even patient care outcomes.”

Alan Lichtin, MD, chair of the MOC working group for the American Society of Hematology (ASH), said the self-paced pathway is a much-needed option, particularly the immediate feedback on test questions. “For years, ASH has been advocating that ABIM move



Dr. Baron

from the traditional sit-down testing to an alternative form of ‘formative’ assessment that has been adapted by other specialty boards,” Dr. Lichtin said in an interview. Anesthesiology and pediatrics have novel testing methods that fit into physicians’ schedules without being so disruptive and anxiety provoking. There is instantaneous feedback about whether the answers are correct or not. It is not useful to study hard for a time-intensive, comprehensive test only to get a summary of what was missed a long time after the test. By that point, the exam material is no longer fresh in one’s mind and therefore the feedback is no longer useful.”

The new pathway is still under development, and ABIM has not said when the option might be launched. In the meantime, the current MOC program and its traditional exam will remain in effect. The board is requesting feedback and comments from physicians about the option. Dr. Baron wrote that more information about the change will be forthcoming in the months ahead.

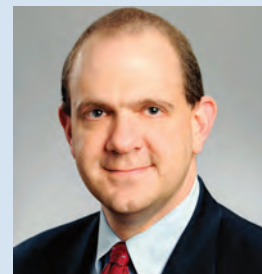
The ABIM announcement comes on the heels of an ongoing legal challenge levied at the board by a group of internists over its MOC process.

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Wildfire smoke particles can enter deep into the lungs // continued from page 1

overloaded with carbon particles that are toxic to those cells, they don't function as well as a first line of defense against bacterial infection, for example."

The new normal of wildfires

Warmer, drier summers in recent years in the western United States and many other regions, attributed by climate experts to global climate change, have produced catastrophic wildfires (PNAS.2016 Oct 18;113[42]:11770-5; Science. 2006 Aug 18;313:940-3). Forest fires in 2018 caused hazardous smoke conditions in Portland, Seattle, Vancouver, and Anchorage and many smaller communities. Such events are expected to be repeated often in the coming years (Int J Environ Res Public Health. 2019 Jul 6;16[13]).

"Smoke is composed primarily of carbon dioxide, water vapor, carbon monoxide, particulate matter, hydrocarbons and other organic chemicals, nitrogen oxides, trace minerals and several thousand other compounds," according to the U.S. Environmental Protection Agency (Wildfire smoke: A guide for public health officials 2019. Washington, D.C.: EPA, 2019). The EPA report noted, "Particles with diameters less than 10 micrometers (particulate matter, or PM₁₀) can be inhaled into the lungs and affect the lungs, heart, and blood vessels. The smallest particles, those less than 2.5 micrometers in diameter (PM_{2.5}), are the greatest risk to public health because they can reach deep into the lungs and may even make it into the bloodstream."

Research on health impact

Wayne Cascio, MD, and his colleagues initiated an epidemiology study to investigate the effects of exposure on cardiorespiratory outcomes in the population affected by fire (Environ Health Perspect. 2011 Oct;119[10]:1415-20). By combining satellite data with syndromic surveillance drawn from hospital records in 41 counties contained in the North Carolina Disease Event Tracking and Epidemiologic Collection Tool, he and his colleagues found that exposure to the peat wildfire smoke led to increases in the cumulative risk ratio for asthma (relative risk, 1.65), chronic obstructive pulmonary disease (RR, 1.73), and pneumonia and acute bronchitis (RR, 1.59). ED visits related to cardiopulmonary symptoms and heart failure also were significantly increased (RR, 1.23 and 1.37, respectively). "That was really the first study to strongly identify a cardiac endpoint related to wildfire smoke exposure," said Dr. Cascio, who directs the EPA's National Health and Environmental Effects Research Laboratory. Those early findings have been replicated in subsequent research about the acute health effects of exposure to wildfire smoke, which contains PM_{2.5} and other toxic substances from structures, electronic devices, and automobiles destroyed in the path of flames, including heavy metals and asbestos. Most of the work has focused on smoke-related cardiovascular and respiratory ED visits and hospitalizations.

A study of the 2008 California wildfire season's impact on ED visits accounted for ozone levels in addition to PM_{2.5} in the smoke. PM_{2.5} inhalation during the wildfires was associated with in-

creased risk of an ED visit for asthma (RR, 1.112; 95% confidence interval, 1.087-1.138) for a 10 mcg/m³ increase in PM_{2.5} and COPD (RR, 1.05; 95% CI, 1.019-1.0825), as well as for combined respiratory visits (RR, 1.035; 95% CI, 1.023-1.046) (Environ Int. 2109 Aug;129:291-8).

Researchers who evaluated the health impacts of wildfires in California during the 2015 fire season found an increase in all-cause cardiovascular



Courtesy Peter Buschmann/US Forest Service

and respiratory ED visits, especially among those aged 65 years and older during smoke days. Rates of all-cause cardiovascular ED visits were elevated across levels of smoke density, with the greatest increase on dense smoke days and among those aged 65 years or older (RR, 1.15; 95% CI, 1.09-1.22). All-cause cerebrovascular visits were associated with dense smoke days, especially among those aged 65 years and older (RR, 1.22; 95% CI, 1.00-1.49). Respiratory conditions also were increased on dense smoke days (RR, 1.18; 95% CI, 1.08-1.28) (J Am Heart Assoc. 2018 Apr 11;7:e007492. doi: 10.1161/JAHA.117.007492).

Unknown long-term effects

When it comes to the long-term effects of wildfire smoke on human health outcomes, much less is known. "We know that there are immediate respiratory health effects from wildfire smoke," said Colleen E. Reid, PhD, of the department of geography at the University of Colorado Boulder. "What's less known is everything else."

Air pollution has been shown to adversely affect health, but whether exposure to wildfire smoke confers a similar risk is less clear. "Until just a few years ago we haven't been able to study wildfire exposure measures on a large scale," said EPA scientist Ana G. Rappold, PhD, a statistician in the environmental public health division of the National Health and Environmental Effects Research Laboratory. "It's also hard to predict wildfires, so it's hard to plan for an epidemiologic study if you don't know where they're going to occur."

Dr. Rappold and colleagues examined cardiopulmonary hospitalizations among adults aged 65 years and older in 692 U.S. counties within 200 km of 123 large wildfires during 2008-2010 (Environ Health Perspect. 2019;127[3]:37006. doi: 10.1289/EHP3860). They observed that an

increased risk of PM_{2.5}-related cardiopulmonary hospitalizations was similar on smoke and non-smoke days across multiple lags and exposure metrics, while risk for asthma-related hospitalizations was higher during smoke days. "One hypothesis is that this was an older study population, so naturally if you're inhaling smoke, the first organ that's impacted in an older population is the lungs," Dr. Rappold said. "If you go to the hospital for asthma, wheezing, or bronchitis, you are taken out of the risk pool for cardiovascular and other diseases. That could explain why in other studies we don't see a clear cardiovascular signal as we have for air pollution studies in general. Another aspect to this study is that the exposure metric was PM_{2.5}, but smoke contains many other components, particularly gases, which are respiratory irritants. It could be that this triggers a higher risk for respiratory [effects] than regular episodes of high PM_{2.5} exposure, just because of the additional gases that people are exposed to."

Another complicating factor is the paucity of data about solutions to long-term exposure to wildfire smoke. "If you're impacted by high-exposure levels for 60 days, that is not something we have experienced before," Dr. Rappold noted. "What are the solutions for that community? What works? Can we show that by implementing community-level resilience plans with HEPA [high-efficiency particulate air] filters or other interventions, do the overall outcomes improve? Doctors are the first ones to talk with their patients about their symptoms and about how to take care of their conditions. They can clearly make a difference in emphasizing reducing exposures in a way that fits their patients individually, either reducing the amount of time spent outside, the duration of exposure, and the level of exposure."

Advice for vulnerable patients

While research in this field advances, the unforgiving wildfire season looms, ensuring more destruction of property and threats to cardiorespiratory health. "There are a lot of questions that research will have an opportunity to address as we go forward, including the utility and the benefit of N95 masks, the utility of HEPA filters used in the house, and even with HVAC [heating, ventilation, and air conditioning] systems," Dr. Cascio said.

The way he sees it, the time is ripe for clinicians and officials in public and private practice settings to refine how they distribute information to people living in areas affected by wildfire smoke. "So, why couldn't the hospital send out a text message or an email to all of the patients with COPD, coronary disease, and heart failure when an area is impacted by smoke, saying, 'Check your air quality and take action if air quality is poor?' Physicians don't have time to do this kind of education in the office for all of their patients. I know that from experience. But if one were to only focus on those at highest risk, and encourage them to follow our guidelines, which might include doing HEPA filter treatment in the home, we probably would reduce the number of clinical events in a cost-effective way."

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INNOVATIVE MEDICINE

Best Practices

Treatment of Unresectable Stage III Non-small Cell Lung Cancer



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Introduction

With a recent renaissance in cancer diagnostics and treatment, there is renewed promise for many who previously held little hope. Lung cancer represents the second most frequently diagnosed cancer, a close second to breast cancer, at 12.9% of expected new cancer cases in 2019.¹ However, the 23.5% death rate predicted for lung cancer outranks breast, prostate, colorectal, and skin melanomas combined.¹ Five-year lung cancer survival rates have increased from 11% in 1975 to more than 20% in 2016.¹ This relatively low rate of survival can probably be explained by the fact that the majority of patients are diagnosed with locally advanced disease (Stage III, disease metastatic to mediastinal or supraclavicular nodes) or advanced disease (Stage IV, disease metastatic to other organs).²⁻⁴ Recent advancements in treatment are proving effective in improving patient outcomes^{5,6}; combined with adherence to screening recommendations and immediate referral to appropriate specialists, earlier diagnosis and staging can help lead to improved outcomes.⁷⁻⁹

Non-small cell lung cancer (NSCLC) constitutes 80% to 85% of lung cancer diagnoses, including histological identification of adenocarcinoma, squamous cell, large cell, and undifferentiated carcinomas.¹⁰⁻¹² Approximately 25% to 30% of patients with NSCLC are diagnosed with locally advanced or Stage III disease.¹² A proportion of these patients may experience the curative benefits of combined chemotherapy and surgery or concurrent chemotherapy and radiation therapy.^{5,13} About 40% of patients with NSCLC are diagnosed with Stage IV disease, and the treatment goal in these patients is to manage symptoms, improve quality of life, and extend survival.^{13,14} Treatment options include systemic chemotherapy, targeted mutation therapies, radiation, immunotherapy, and on occasion surgery.⁷ It is vital that we increase early diagnosis, accurate staging, and referral to the appropriate specialists in lung cancer to ensure that treatment is optimized and more lives are potentially saved.⁷

Screening and Diagnosis

Unlike with breast, prostate, and colorectal cancers, systematic screening for lung cancer is not a well-established population-based practice, and its role is not fully grasped by primary caregivers.¹⁵ Risk factors such as history of tobacco use and exposure to second-hand smoke are common knowledge, but other environmental exposures (diesel smoke, pollution,

and other cancer-causing agents) are difficult to quantify.^{16,17} Populations with lifestyles with higher exposure to these factors are generally more reticent to intervention and skeptical of the benefits of treatment, while others may be concerned that radiation-based screening techniques contribute to the risk.¹⁵ In addition to patient perceptions that defer intervention, presenting symptoms of cough and dyspnea are frequently confounded with other respiratory conditions, creating a delay in early detection and staging.⁹ Even further delays have been seen when patients present with more generalized symptoms like fatigue or bone or joint pain.⁹

Based on the National Lung Screening Trial (NLST),¹⁸ the American College of Chest Physicians (ACCP) has published recommendations that low-dose computerized tomography (LDCT) scans be performed annually on patients meeting the following criteria: (1) 30 pack-year current smoker or former smoker between the ages of 55 and 74 years, (2) former smokers who have quit within the past 15 years, and (3) no comorbidities that potentially preclude curative treatment benefit.¹⁵ The National Comprehensive Cancer Network® (NCCN®) also encourages patients to seek yearly screening if they are 50 years or older, have a 20 or more pack-year smoking history, and have other known risk factors besides second-hand smoke exposure, such as radon exposure.¹⁹ Screening with LDCT, in select patients at high risk for lung cancer, decreased the relative risk of death from lung cancer by 20% when compared with chest radiography.¹⁸ As such, efforts are being made to educate general practitioners and the public about this tremendous benefit.^{15,19,20}

The goal of screening is to identify a lung cancer in the earliest possible stage, which, as **Table 1** demonstrates, directly improves survivability.¹⁹ However, imaging alone does not provide accurate staging, and once lung cancer is suspected, time is of the essence in ensuring no further progression. Various target time recommendations have been published advocating for improved wait times across the care spectrum, ranging from 30 to 52 days of median wait time from diagnosis to first treatment.^{23,24} Yet one Canadian study showed that despite the recommended time of 2 weeks between symptom onset and diagnosis, the actual median time to diagnosis was 4.5 months.⁹ It has been estimated that every 4 weeks between scans represents the potential for a 13% progression.²⁵ Kasymjanova et al describe 2 studies

and a meta-analysis demonstrating that increased wait times impart a negative effect on recurrence and survival.²³ In their own study, it was noted that reduced wait times particularly benefited Stage III NSCLC survival.²³

Because pulmonologists may be the first specialist a patient sees, they are relied upon to diagnose, stage, and coordinate care for many patients with lung cancer.²⁶ Because Stage III NSCLC is a curative intent setting,^{13,27} it is of particular importance to coordinate more complicated surgical, radiation, and chemotherapy care for these patients as soon as the diagnosis and stage have been ascertained.⁷ While initial chest computed tomography or positron emission tomography (PET) scans often determine tumor size(s) and location(s), and presence of hilar or mediastinal nodes and extrathoracic lesions (excluding the brain), these studies cannot be the sole factors used in staging, and they falsely overstage 19% of the time and understage 13% of the time.²⁸ The ACCP guidelines recommend magnetic resonance imaging (MRI) of the brain for patients with clinical Stage III or IV disease with or without symptoms of intracranial disease,²⁹ whereas NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®) recommend staging brain MRI in patients with clinical Stage IB (optional), IIA/B, IIIA/B/C and IV.³⁰

Diagnostic procedures to obtain accurate histological diagnosis and staging and adequate tissue samples for molecular testing must be considered, ideally with input from a multidisciplinary team (MDT) composed of pulmonologists, thoracic surgeons, and radiology specialists who are board certified and have expertise in thoracic oncology whenever any stage of NSCLC is suspected.³⁰ PET imaging can be used to identify the optimal biopsy site that produces the highest yield, is minimally invasive, and is most likely to confer the highest staging.³⁰ Whenever possible, procedures should be combined (bronchoscopy and endobronchial ultrasound with needle aspiration of lymph nodes) to improve time to diagnosis and clinical staging.³⁰ Invasive mediastinal staging is recommended before surgical resection.³⁰ The organization of lung cancer care requires development of a multidisciplinary program committed but not limited to the expeditious coordination of the patient's care among various disciplines to avoid unnecessary tests and procedures, delay in care, costly care, and patient frustration and anxiety.³¹ Multidisciplinary care has been shown to decrease time to diagnosis and improve referral for appropriate treatment.³² In particular, patients with Stage III NSCLC are more



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TABLE 1. Summary of NSCLC Staging & Prognosis^{3,21,22}

Stage	TNM Classification ²¹ (Tumor, Node, Metastases)	Nodal Zones & Stations ^{3,22}	Treatment/Goal ²²	5-Year Survival ²¹
IA ₁	T1a or T1a(mi), N0, M0	N1 = Hilar Zone if ipsilateral • Station 10 (Hilar nodes) Peripheral Zone if ipsilateral • Station 11 (Interlobar nodes) • Station 12 (Lobar Nodes) • Station 13 (Segmental Nodes) • Station 14 (Subsegmental Nodes) N2 = Lower Zone if ipsilateral • Station 8 (Paraesophageal nodes) • Station 9 (Pulmonary ligament nodes) Subcarinal Zone if ipsilateral • Station 7 (Subcarinal nodes) Aortopulmonary Zone • Station 5 (subaortic & aortopulmonary nodes) • Station 6 (para-aortic nodes) Superior Mediastinal Zone • Station 2 (Upper paratracheal nodes) • Station 3 (Prevascular & retrotracheal nodes) • Station 4 (Lower paratracheal nodes) N3 = Supraclavicular Zone • Station 1 (Low cervical, supraclavicular, sternal notch nodes) • contralateral mediastinal, contralateral hilar, ipsilateral/contralateral scalene, superclavicular nodes	Surgery or radiation	92%
IA ₂	T1b, N0, M0		Surgery ± radiation, OR Radiation	83%
IA ₃	T1c, N0, M0			77%
IB	T2a, N0, M0			68%
IIA	T2b, N0, M0			60%
IIB	T1a-c, N1, M0 <or> T2a-b, N1, M0 <or> T3, N0, M0	N1 generally resectable N2 heterogeneous resectability	Surgery ± Chemotherapy ± Radiation	53%
IIIA	T1a-c, N2, M0 <or> T2a-b, N2, M0 <or> T3-4, N1, M0 <or> T4, N1, M0		Surgery ± Chemotherapy ± Radiation	36%
IIIB	T3, N2, M0 <or> T4, N2, M0	N2 = heterogeneous resectability N3 generally non-resectable	Radiation ± Chemotherapy ± Immunotherapy	36-41% [†]
IIIA	T1a-c, N2, M0 <or> T2a-b, N2, M0 <or>		Radiation ± Chemotherapy ± Immunotherapy	24-26% [†]
IIIB	T1a-c, N3, M0 <or> T2a-b, N3, M0 <or> T3, N2, M0 <or> T4, N2, M0			12-13% [†]
IIIC	T3-4, N3, M0			
IVA	Any T, Any N, M1a-b		Palliative Care with Systemic Therapy	0%
IVB	Any T, Any N, M1c			0%

Abbreviations: M1a, separate tumor contralateral lobe or primary tumor with pleural/pericardial nodules or malignant effusions; M1b, single extrathoracic mass; M1c, multiple extrathoracic masses; mi, minimally invasive adenocarcinoma.

T1a ≤ 1cm; T1b >1cm, ≤ 2cm; T1c >2cm, ≤ 3cm; T2a >3cm, ≤ 5cm; T2b >4cm, ≤ 5cm; T3 >5cm, ≤ 7cm; T4 >7cm.

[†]Reflects changes in 5-year survival of all stage III NSCLC when staging included pathology information.

likely to receive appropriate treatment when referred to oncology specialists.⁷ Still, data suggest that up to 20% of patients diagnosed with Stage III NSCLC are never evaluated by an oncologist.³³

The tumor, node, metastasis (TNM) system for staging has been used since 1944.⁸ Now governed by the International Association for the Study of Lung Cancer (IASLC), the eighth edition took effect in 2017.²¹ Several changes from the seventh edition, including new TNM definitions and addition of categories, have caused shifts in staging, with a greater emphasis on tumor size and invasion of surrounding tissues.³ As a result, Stage III now includes subtype C (T3-T4, N3, M0), which is still treated in a curative intent setting.²¹ Additionally, nodal zones were further broken down into more specific stations that clearly define anatomic landmarks within each zone, as this too proved to be associated with prognosis.³ Differentiating Stage IIIC from Stage IVA has provided more patients the opportunity to be treated in a curative intent setting, as further data collection and new research are expanding within each subtype and allowing for individualized treatment approaches.^{3,21}

Clinically, the distinction between resectable and unresectable Stage III

disease is of significance because unresectable Stage III does not afford a treatment path as well-established as resectable disease (surgery).³⁴ Unresectable generally includes Stage IIIA tumors (T1-T2 tumors with multiple positive ipsilateral mediastinal nodes), often described as bulky or extensive; Stage IIIB (T1-T2 tumors with positive contralateral mediastinal or supraclavicular nodes or T3-T4 tumors with positive ipsilateral mediastinal nodes); and Stage IIIC (T3-T4 tumors with positive contralateral mediastinal or supraclavicular nodes).¹¹

Treatment of Stage III NSCLC

Patients clinically determined to have resectable Stage III NSCLC are candidates for a variety of treatment options, none of which have proven to be superior.¹¹ The 2019 NCCN Guidelines[®] suggest the following course for resectable Stage III NSCLC: (1) Preoperative chemotherapy (CT) and radiation (CTR), or preoperative CT followed by post-operative RT (split-panel decision); and (2) surgery, using minimally invasive techniques where possible.³⁰ The panel acknowledges that controversy remains regarding the sequencing of surgery, chemotherapy, and radiation techniques.

The majority of patients with Stage III NSCLC have unresectable disease.³⁵ Platinum-based CT has been preferred over other chemotherapeutic modalities for over 3 decades.³⁶ Evidence supports its use as part of definitive CRT along with a minimum of 60 Gy in escalated doses; concurrent treatment is currently preferred over sequential in all histological findings.³⁰ Accelerated RT alone imparts some benefit to those who refuse CT.¹¹

Severe immune-mediated adverse reactions are associated with all immune checkpoint inhibitors, including pneumonitis, causing discontinuation.³⁷ A recent retrospective single-center study suggests that patients who are on corticosteroids for cancer-unrelated indications have similar outcomes on immunotherapy as patients who are receiving 0 to < 10 mg of prednisone.³⁷ However, additional mechanistic studies as well as prospective clinical trials are needed to identify whether the use of corticosteroids affects specific aspects of the immune system necessary for immunotherapy activity. Optimal treatment duration for immune checkpoint inhibitors requires further study, and their use in patients with autoimmune disorders and a past organ transplantation should be avoided.³⁸

Conclusion

Locally advanced and metastatic NSCLC patients have benefitted from intensive research into immunologic approaches to treatment. Accurate diagnosis and staging are critical, particularly in the differentiation between Stage III, which is treated with curative intent, and Stage IV, which is metastatic. CRT is the current standard of care for unresectable Stage III disease and has shown improvement in overall survival, while the introduction of immunotherapy following CRT treatment can be discussed as a treatment option. To reap the benefits of these advances in treatment, patients with suspected or confirmed lung cancer should be managed by an MDT that includes a pulmonologist, thoracic surgeon, and medical and radiation oncologists, and referral for appropriate treatment of Stage III and IV NSCLC is crucial to improving patient outcomes.

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Pulegone levels in mint-flavored e-liquids, smokeless tobacco products exceed FDA limits

BY LUCAS FRANKI

MDedge News

A group of mint- and menthol-flavored e-liquids and smokeless tobacco products contained significantly more pulegone – a known carcinogen that causes hepatic carcinomas, pulmonary metaplasia, and other neoplasms – than the Food and Drug Administration considers acceptable, according to new findings.

Pulegone, an oil extract from mint plants such as peppermint, spearmint, and pennyroyal, was banned as a food additive by the agency in 2018, and the tobacco industry has taken steps to minimize pulegone levels in cigarettes because of the toxicity concerns.

Studies from the Centers for Disease Control and Prevention, however, have indicated that mint- and menthol-flavored e-cigarette liquids and smokeless tobacco products marketed in the United States contain substantial amounts of the substance, Sairam V. Jabba, DVM, PhD, and Sven-Eric Jordt, PhD, said in a research letter published in *JAMA Internal Medicine*.

Dr. Jabba and Dr. Jordt, both with the de-

partment of anesthesiology at Duke University, Durham, N.C., calculated the margin of exposure in five e-liquids (V2 Menthol, V2 Peppermint, Premium Menthol, South Beach Smoke Menthol, and South Beach Smoke Peppermint) and one smokeless tobacco product (Skoal Xtra Mint snuff) by dividing the no-observed adverse event level (13.39 mg/kg of bodyweight per day) by the mean human exposure to e-liquids or smokeless tobacco. The FDA considers margin-of-exposure values of 10,000 or less to require mitigation strategies.

The six products included in the analysis had pulegone concentration levels ranging from 25.7 to 119.0 mcg/g (a menthol cigarette has a pulegone concentration of 0.037-0.290 mcg/g). Based on those levels, light daily use (5 mL e-liquid, 10 g smokeless tobacco, half a pack of cigarettes) exposed e-cigarette users to 44-198 times more pulegone, compared with menthol cigarettes, and exposed smokeless tobacco users to 168-1,319 times as much pulegone. The margin of exposure ranged from 1,298 to 6,012, all below the threshold the FDA deems acceptable.

For heavy daily use (20 mL e-liquid, 30 g

smokeless tobacco, two packs of cigarettes), e-cigarette users were exposed to 282-1,608 times more pulegone, compared with menthol cigarettes; smokeless tobacco users were exposed to 126-990 times more pulegone. The margin of exposure ranged from 325 to 1,503.

The study findings “appear to establish health risks associated with pulegone intake and concerns that the FDA should address before suggesting mint- and menthol-flavored e-cigarettes and smokeless tobacco products as alternatives for people who use combustible tobacco products,” Dr. Jabba and Dr. Jordt concluded.

The study was funded by a grant from the National Institute of Environmental Health Sciences. Dr. Jordt reported receiving grants from the NIEHS and the National Institute on Drug Abuse, personal fees from Hydra Biosciences and Sanofi, and nonfinancial support from GlaxoSmithKline. Dr. Jabba reported no disclosures.

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SOURCE: Jabba SV, Jordt S-E. *JAMA Intern Med*. 2019 Sep 16. doi: 10.1001/jamainternmed.2019.3649.

Tocilizumab preserves lung function in systemic sclerosis

BY SARA FREEMAN

MDedge News

MADRID – Tocilizumab (Actemra) preserved lung function in patients with early systemic sclerosis (SSc), according to a secondary endpoint analysis of the phase 3, double-blind, randomized, controlled focuSSced trial.

After 48 weeks, a significantly lower proportion of patients treated with tocilizumab than placebo experienced any decline in lung function from baseline (50.5% versus 70.3% ($P = .015$), as defined by the percentage increase in predicted forced vital capacity (%pFVC). When only patients with interstitial lung disease (ILD) were considered, the respective percentages were 51.7% and 75.5% ($P = .003$).

In SSc-ILD patients, a clinically meaningful decline of 10% or more of the %pFVC in lung function was seen in 24.5% given placebo but in just 8.6% of those treated with tocilizumab.

“ILD is a major complication of scleroderma; it has high morbidity and mortality ... and it’s largely irreversible,” Dinesh Khanna, MD, said at the European Congress of Rheumatology.

“In this day and age, when we treat



Dr. Dinesh Khanna spoke at the European Congress of Rheumatology, on the use of tocilizumab. Watch the interview at <https://tinyurl.com/y3ydsecu>.

ILD, we wait for a patient to develop clinical ILD,” added Dr. Khanna, director of the scleroderma program at the University of Michigan, Ann Arbor. Clinical ILD can be defined by symptoms, abnormal pulmonary function tests, and marked abnormalities on high-resolution computed tomography (HRCT) scans. He indicated that, if improving ILD was not possible, then the next best thing would be to stabilize the disease and ensure there was no worsening in lung function.

As yet, there are no disease-modifying treatments available to treat SSc but there are “ample data that interleukin-6 plays a very important

role in the pathogenesis of scleroderma,” Dr. Khanna observed. Tocilizumab is a humanized monoclonal antibody against the interleukin-6 receptor.

Data from the phase 2 faSScinate trial showed initial promise for the drug in SSc where a numerical, but not statistically significant, improvement in skin thickening was seen, and the results had hinted at a possible benefit on lung function (*Lancet*. 2016 Jun 25;387:2630-40).

However, in the phase 3 focuSSced trial, there was no statistically significant difference in the change from baseline to week 48 modified Rodnan skin score (mRSS)

between tocilizumab and placebo, which was the primary endpoint. The least-square mean change in mRSS was -6.14 for tocilizumab and -4.41 for placebo ($P = .0983$).

A total of 205 patients with SSc were studied and randomized, 1:1 in a double-blind fashion, to receive either a once-weekly, subcutaneous dose of 162 mg tocilizumab or a weekly subcutaneous placebo injection for 48 weeks.

For inclusion in the study, patients had to have SSc that met American College of Rheumatology and European League Against Rheumatism (EULAR) criteria and be diagnosed less than 60 months previously. Patients had to have an mRSS of 10-35 units and active disease with one or more of the following: C-reactive protein of 6 mg/L or higher; erythrocyte sedimentation rate of 28 mm/h or higher; and platelet count of 330×10^9 L.

Roche/Genentech sponsored the study. Dr. Khanna acts as a consultant to Roche/Genentech and eight other pharmaceutical companies. He owns stock in Eicos Sciences.

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SOURCE: Khanna D et al. *Ann Rheum Dis*. Jun 2019;78(Suppl 2):202-3, Abstract OP0245. doi: 10.1136/annrheumdis-2019-eular.2120

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Benefits of peanut desensitization may not last

BY HEIDI SPLETE

MDedge News

About a third of peanut-allergic patients given oral immunotherapy (OIT) passed a peanut challenge when the therapy was reduced, based on data from a phase 2 randomized trial of individuals with confirmed peanut allergies.

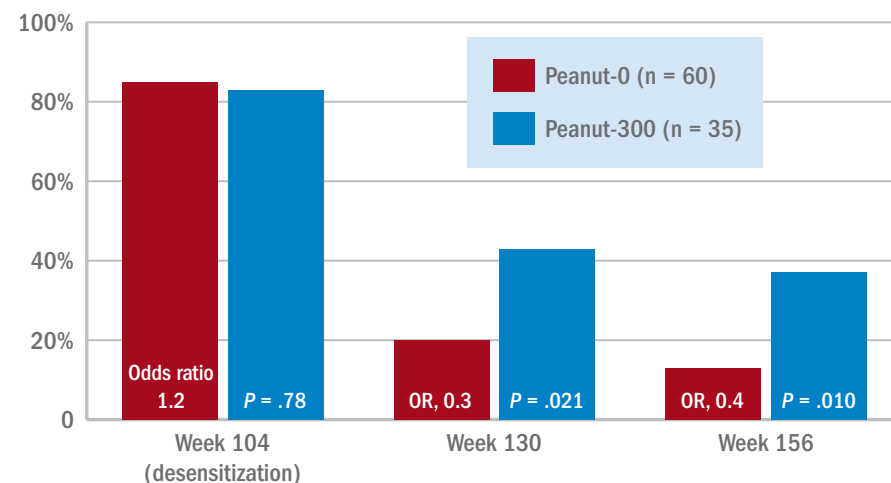
Previous studies have shown that desensitization to peanuts can be successful, but sustained response to oral immunotherapy after treatment reduction or discontinuation has not been well studied, wrote R. Sharon Chinthrajah, MD, of Stanford (Calif.) University, and colleagues.

“We found that OIT with peanut was able to desensitize people with peanut allergy to 4,000 mg of peanut protein, but that discontinuation of peanut, or even a reduction to 300 mg daily, increased the likelihood of regaining clinical reactivity to peanut,” they wrote. “With peanut allergy therapies in varying stages of clinical development, and some nearing [Food and Drug Administration] approval, vital questions remain regarding the durability of treatment effects and the appropriate maintenance doses.”

In the Peanut Oral Immunotherapy Study: Safety Efficacy and Discovery (POISED), published in *The Lancet*, the researchers randomized 120 participants to three groups:

- 60 patients built up to a maintenance dose of 4,000 mg of peanut protein for 104 weeks followed by

OIT patients who passed food challenge to peanut



Note: Based on data from a phase 2 randomized trial of peanut oral immunotherapy (OIT).

Source: *Lancet*. 2019 Sep 12. doi: 10.1016/S0140-6736(19)31793-3

- total discontinuation (peanut-0).
- 35 patients built up to a maintenance dose of 4,000 mg of peanut protein for 104 weeks followed by a 300-mg maintenance dose of peanut protein in the form of peanut flour (peanut-300).
- 25 patients had an oat flour placebo.

All participants were trained on how and when to use epinephrine autoinjector devices to treat allergic symptoms such as respiratory problems (cough, shortness of breath, or change in voice), widespread hives or erythema, repetitive vomiting, persistent abdominal pain, angioedema of the face, or feeling faint.

The primary outcome was passing a double-blind, placebo-controlled,

food challenge (DBPCFC) to 4,000 mg of peanut protein, which was measured at baseline and at weeks 104, 117, 130, 143, and 156.

Overall, 35% of the peanut-0 group passed the challenge at 104 and 117 weeks, compared with 4% of the placebo group. At week 156 after discontinuing OIT, 13% of the peanut-0 group met the DBPCFC challenge, compared with 4% of the placebo group. However, 37% of participants randomized to a reduced peanut protein dose of 300 mg passed the challenge at 156 weeks, suggesting that more data are needed on optimal maintenance dosing strategies.

Baseline demographics were similar across all groups. The median age at

study enrollment was 11 years and the median allergy duration was 9 years. The most common adverse events were mild gastrointestinal and respiratory problems. Adverse events decreased over time in all three groups.

“Higher levels of peanut-specific IgE to total IgE ratio, peanut sIgE, Ara h 1, Ara h 2, and Ara h 1 IgE to peanut-specific IgE ratio at baseline in participants were associated with increased frequencies of adverse events during active peanut OIT,” the researchers noted.

The study findings were limited by several factors including the ability of participants to tolerate 4,000 mg of peanut protein after achieving a maintenance dose but conducting serial testing only for those who passed the challenge. In addition, the results may be limited to peanut and not generalizable to other food allergies, the researchers said.

However, the results suggest that OIT remains a promising treatment for peanut allergies, and the association of biomarkers with clinical outcomes “might help the practitioner in identifying good candidates for OIT and those individuals who warrant increased vigilance against allergic reactions during OIT,” they said.

The National Institutes of Health supported the study. The researchers had no financial conflicts to disclose.

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SOURCE: Chinthrajah RS et al. *Lancet*. 2019 Sep 12. doi: 10.1016/S0140-6736(19)31793-3.

Allergy immunotherapy may modify asthma severity

BY MARK S. LESNEY

MDedge News

The use of a grass-based allergy immunotherapy (AIT) lowered the risk of progression from milder to more severe asthma, according to the results of a large, real-world, industry-sponsored, observational study.

The researchers analyzed a cohort of 1,739,440 patients aged 12 years and older using 2005-2014 data from a statutory health insurance database in Germany. From this population, 39,167 individuals aged 14 years or older were classified as having incident asthma during the observation period and were included in the study.

The severity of asthma was classified according to the treatment steps recommended by the Global Initiative for Asthma (GINA).

Among these, 4,111 patients (10.5%) received AIT. AIT use was associated with a significantly decreased likelihood of asthma progression from GINA step 1 to step 3 (hazard ratio, 0.87; 95%



confidence interval, 0.80-0.95) and GINA step 3 to step 4 (HR, 0.66; 95% CI, 0.60-0.74).

Medications for GINA step 2 (3.5%) and GINA step 5 (0.03%) were rarely prescribed, so the researchers could not analyze the transition between GINA steps 1 and 2, step 2 and 3, and step 4 and 5.

A total of 8,726 patients had at least one transi-

tion between GINA steps 1, 3, or 4, and 1,085 had two transitions, though not all 39,167 patients were under risk of severity progression into all GINA steps, according to the authors.

The findings are consistent with earlier studies that indicate grass-based immunotherapy can effectively treat asthma symptoms and potentially asthma progression (*J Allergy Clin Immunol*. 2012;129[3]:717-25; *J Allergy Clin Immunol*. 2018;141[2]:529-38).

“This study indicates that AIT may modify the course of asthma. Our study supports the assumption that treatment with AIT may prevent the progression from mild to more severe asthma,” the authors concluded.

The study was financially supported by ALK-Abelló; several of the authors were also employees of or received funding from the company.

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SOURCE: Schmitt J et al. *Allergy*. 2019. doi: 10.1111/all.14020.

Vaping habit may lead to nicotine addiction in teens

BY RICHARD FRANKI

MDedge News

Adolescents' past 30-day use of e-cigarettes more than doubled from 2017 to 2019, and in 2019 almost 12% of high school seniors reported that they were vaping every day, according to data from the Monitoring the Future surveys.

Daily use – defined as vaping on 20 or more of the previous 30 days – was reported by 6.9% of 10th-grade and 1.9% of 8th-grade respondents in the 2019 survey, which was the first time use in these age groups was assessed. “The substantial levels of daily vaping suggest the development of nicotine addiction,” Richard Miech, PhD, and associates said Sept. 18 in the New England Journal of Medicine.

From 2017 to 2019, e-cigarette use over the previous 30 days increased from 11.0% to 25.4% among 12th graders, from 8.2% to 20.2% in 10th graders, and from 3.5% to 9.0% of 8th graders.

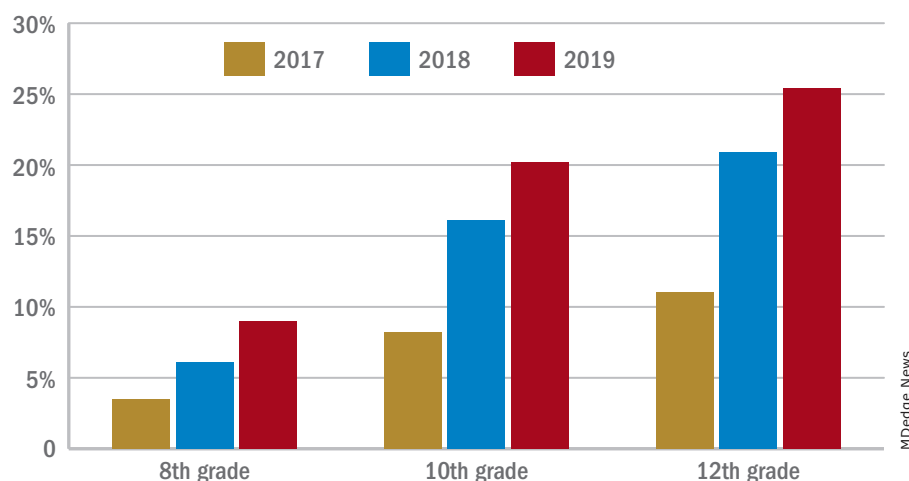
By 2019, over 40% of 12th-grade students reported ever using e-cigarettes, along with more than 36% of 10th graders and almost 21% of 8th graders. Corresponding figures for past 12-month use were 35.1%, 31.1%, and 16.1%, they reported.

The analysis was funded by a grant from the National Institute on Drug Abuse to Dr. Miech.

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SOURCE: Miech R et al. N Engl J Med. 2019 Sep 18. doi: 10.1056/NEJMc1910739.

Prevalence of vaping among adolescents in the past 30 days



Note: Based on data from the Monitoring the Future surveys.

Source: N Engl J Med. 2019 Sep 18. doi: 10.1056/NEJMc1910739

Serum testosterone and estradiol levels associated with current asthma in women

BY THERESE BORDEN

MDedge News

Elevated serum levels of circulating sex hormones were found to be associated with lower odds of asthma in women, possibly explaining in part the different prevalence of asthma in men and women, according to the findings of a large cross-sectional population based study.

Yueh-Ying Han, PhD, of the Children's Hospital of Pittsburgh and colleagues investigated the role of free testosterone and estradiol levels and current asthma among adults. The impact of obesity on that association was also examined. The investigators analyzed data from 7,615 adults (3,953 men and 3,662 women) who participated in the 2013-2014 and 2015-2016 U.S. National Health and Nutrition Examination Survey. The data included health interviews, examination components, and laboratory tests on each patient. Serum samples were analyzed by the division of laboratory sciences of the Centers for Disease Control and Prevention. Logistic regression was used for the multivariable analysis of sex hormone levels (as quartiles) and current asthma, and the analysis was done separately on men and women. Pregnant women were excluded, in addition to individuals with incomplete data. The exclusions tended to be Hispanic ethnicity, former smokers, lower income, and lack private insurance. The overall prevalence of current asthma in the sample was 9% (6% in men and 13% in women).

Three models were generated based on serum levels in women and in men.

For model 1 (unadjusted for estradiol), women whose serum testosterone levels were in the second and fourth quartiles had 30%-45% significantly lower odds of having current asthma than those whose serum testosterone level was in the lowest quartile. Among men, those whose serum testos-

terone levels were in the second and fourth quartiles had 12%-13% lower odds for current asthma.

For model 2 (unadjusted for free testosterone), women whose serum estradiol levels were in the third quartile had 34% significantly lower odds of having current asthma than those whose estradiol levels were in the lowest quartile. The findings were similar for men, that is, those whose serum

The investigators wrote, “Androgens such as testosterone may reduce innate and adaptive immune responses, while estrogen and progesterone may enhance T-helper cell type 2 allergic airway inflammation.”

estradiol levels were in the third quartile had 30% lower odds for having asthma, compared with those with in the lowest quartile.

For model 3 (a multivariable model including serum levels of both estradiol and free testosterone), women whose serum testosterone levels were in the second and fourth quartiles had 30% and 44% lower odds of current asthma than those whose serum testosterone levels were in the lowest quartile. But in this multivariable model, the association between serum estradiol and current asthma was not significant. Among men (models 1-3), the magnitude of the estimated effect of serum testosterone and serum estradiol on current asthma was similar to that observed in female participants, but neither serum testosterone nor serum estradiol was significantly associated with current asthma.

The investigators then analyzed the impact of obesity on the relationship between serum hormone levels and obesity. Obesity was defined as body mass index equal to or greater than 30 kg/m². A total of 1,370 men and 1,653 women were

included in this analysis. In multivariable analyses of the obese participants, adjustment without (model 1) and with (model 3) serum estradiol, serum free-testosterone levels in the highest (fourth) quartile were significantly associated with reduced odds of asthma in obese women. In multivariable analyses without (model 2) and with (model 3) testosterone, serum estradiol levels above the first quartile were significantly associated with reduced odds of current asthma in obese women.

In contrast to the results in obese women, neither serum free testosterone nor serum estradiol was significantly associated with current asthma in obese men or nonobese women.

Dr. Han and coauthors suggested a possible mechanism of the role of sex hormones in asthma. “Androgens such as testosterone may reduce innate and adaptive immune responses, while estrogen and progesterone may enhance T-helper cell type 2 allergic airway inflammation.”

They concluded: “We found that elevated serum levels of both free testosterone and estradiol were significantly associated with reduced odds of asthma in obese women, and that elevated levels of serum estradiol were significantly associated with reduced odds of asthma in nonobese men. Our findings further suggest that sex steroid hormones play a role in known sex differences in asthma among adults.”

One coauthor has received research materials from Merck and GlaxoSmithKline (inhaled steroids), as well as Pharmavite (vitamin D and placebo capsules), to provide medications free of cost to participants in National Institutes for Health-funded studies, unrelated to the current work. The other authors reported no conflicts of interest.

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SOURCE: Han Y-Y et al. J Respir Crit Care Med. 2019 Sep 16. doi: 10.1164/rccm.201905-0996OC.

Dapagliflozin moves from antidiabetic to HF drug

BY MITCHEL L. ZOLER

MDedge News

PARIS – Treatment with the SGLT2 inhibitor dapagliflozin produced a statistically significant 27% drop in cardiovascular death or heart failure events in patients with existing heart failure with reduced ejection fraction and no diabetes, results that in a stroke changed the status of dapagliflozin from fundamentally a drug that treats diabetes to a drug that treats heart failure.

“Dapagliflozin offers a new approach to the treatment of heart failure with reduced ejection fraction” (HFrEF), John McMurray, MD, said at the annual congress of the European Society of Cardiology.

The results he reported from the DAPA-HF (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure) trial showed statistically significant benefits when adding dapagliflozin to guideline-directed therapy for a list of outcomes that include a 17% drop in all-cause death compared with placebo, an 18% fall in cardiovascular death, and a 25% relative reduction in total heart failure hospitalizations plus cardiovascular deaths during a median follow-up of just over 18 months. The primary endpoint of the reduction in cardiovascular death, first heart failure hospitalization, or an urgent heart failure visit fell by 25% in the enrolled patients with diabetes (45% of the study population, all with type 2 diabetes), and by 27% in the remaining patients who had no diabetes, showing that the presence of diabetes had no impact on the heart failure benefit from dapagliflozin. The absolute reduction in the primary endpoint was about 5%, with a number needed to treat of 21 to prevent one primary endpoint during 18 months of treatment.



Dr. Mann

Dr. McMurray’s report of the primary endpoint and the finding that the drug was as effective in patients without diabetes as in those with diabetes were met with loud applause by the packed congress audience. The efficacy results also showed that 58% of patients on dapagliflozin had a clinically meaningful (5-point



Dr. John McMurray

or greater) increase in their quality of life score on the Kansas City Cardiomyopathy Questionnaire after 8 months on treatment compared with a 51% rate in the placebo patients, a statistically significant difference.

The safety results showed no new signals for a drug that already has regulatory approval but was being used in a novel population. The rate of major hypoglycemia was virtually nonexistent, 0.2%, and identical in both treatment arms. All adverse events occurred at roughly equal rates in the dapagliflozin and placebo groups, with a 5% rate of adverse events leading to study discontinuation in both arms, and a serious adverse event rate of 38% in the dapagliflozin patients and 42% in the placebo patients. The rate of worsening renal function was less than 2% in both arms and not statistically different.

“This is as close to a home run as you see in heart failure treatment,” commented Douglas L. Mann, MD, professor of medicine at Washington University, St. Louis, and a heart failure clinician and researcher.

DAPA-HF “is a landmark trial. It took a diabetes drug and used it in patients without diabetes, a concept that would have been considered outlandish 5 years ago. Scientifically it’s huge,” commented Deepak L. Bhatt, MD, professor of medicine at Harvard Medical School in Boston.

The DAPA-HF results were another step in the remarkable journey toward heart failure intervention taken by the SGLT2 (sodium glucose cotransport 2) inhibitor class of drugs that includes dapagliflozin as well as canagliflozin (Invokana) and empagliflozin (Jardiance), a path that began 4 years ago with the report of empagliflozin’s unexpected efficacy for reducing cardiovascular death and heart failure hospitalizations in a large cardiovascular-safety study,

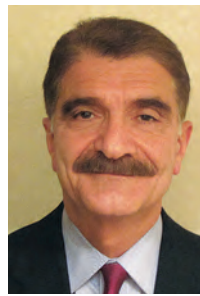


Dr. Deepak L. Bhatt

VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments:

Interesting study with important findings that appear to be a game changer in the treatment of HFrEF.



EMPA-REG OUTCOME (N Engl J Med. 2015 Nov 26;373[22]:2117-28). Subsequent reports showed similar effects benefiting heart failure and survival for canagliflozin and dapagliflozin, and now with DAPA-HF the evidence extended the benefit to heart failure patients regardless of whether they have diabetes. Additional studies now in progress are exploring the same question for empagliflozin and canagliflozin.

The results from DAPA-HF are likely a class effect for all these SGLT2 inhibitors, suggested Dr. McMurray in a video interview, a view shared by several other experts. He cautioned clinicians against using dapagliflozin to treat patients with heart failure with reduced ejection fraction but without diabetes until this indication receives regulatory approval, and even then using dapagliflozin or other SGLT2 inhibitors this way may take some getting used to on the part of cardiologists and other clinicians.

“The results put dapagliflozin in the same league as [standard HFrEF drugs], but using it will require a shift in thinking. “I’m sure most cardiologists are not familiar with the SGLT2 inhibitors; we’ll have to educate them,” conceded Dr. McMurray, professor of medical cardiology at the University of Glasgow. However,

other aspects of dapagliflozin and this drug class in general may make the SGLT2 inhibitors particularly attractive and spur their use once labeling changes.

The adverse-event profile seen in DAPA-HF looked very “clean,” said Dr. Mann, especially compared with the other medical classes recommended in guidelines for patients with HFrEF: the angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, and mineralocorticoid-receptor antagonists such as spironolactone, and the angiotensin receptor-neprilysin inhibitor (ARNI) sacubitril-valsartan (Entresto). “I think dapagliflozin will have a huge uptake [for treating HFrEF], because it will be easy for primary care physicians to prescribe. It will be easier to use than traditional heart failure medications.” Once approved for heart failure use, Dr. Mann predicted a standard dosing regimen for HFrEF patients of an ACE inhibitor, ARB or ARNI, a beta-blocker, a mineralocorticoid-receptor antagonist, and an SGLT2 inhibitor. He suggested that this large and cumbersome collection of medications could conceivably be simplified into a poly pill.

DAPA-HF was sponsored by AstraZeneca, the company that markets dapagliflozin (Farxiga). AstraZeneca paid Glasgow University to cover Dr. McMurray’s salary during the time he spent working as principal investigator of DAPA-HF. Dr. McMurray had no other relevant disclosures. Dr. Mann has been a consultant to Bristol-Myers Squibb, LivaNova, Novartis, and Tenaya Therapeutics. Dr. Bhatt has received research funding from AstraZeneca, and he has served as a consultant to or received research funding from several other companies.

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Women may be treated with lower doses of HF drugs

BY RANDY DOTINGA

MDedge News

Men and women react differently to common drugs used to treat heart failure with reduced ejection fraction (HFrEF), according to findings from a new European study, and women may be able to safely cut their doses in half and get the same level of relief as that provided by larger doses.

“This study ... brings into question what the true optimal medical therapy is for women versus men,” the study authors, led by Bernadet T. Santema, MD, of the University Medical Center Groningen (the Netherlands), wrote in an article published in the *Lancet*.

Dr. Santema and colleagues noted that current guidelines for the use of ACE inhibitors or angiotensin-receptor blockers (ARBs) and beta-blockers for men and women with heart failure do not differentiate between the genders, despite findings showing that, “with the same dose, the maximum plasma concentrations of ACE inhibitors, ARBs, and beta-blockers

were up to 2.5 times higher in women than in men.”

In addition, the researchers wrote, women are much more likely than men to suffer side effects from medications, and the effects tend to be more severe.



Dr. Santema

HFrEF accounts for an estimated 50% of the 5.7 million patients with heart failure in the United States (Nat Rev Dis Primers. 2017 Aug 24. doi: 10.1038/nrdp.2017.58; Card Fail Rev. 2017;3[1]:7-11).

For the new study, researchers launched an ad hoc analysis of the findings of a prospective study of HFrEF patients in 11 European countries (1,308 men and 402 women) who took drugs in the three classes. Patients were receiving sub-optimal medication doses at the start of the study, and physicians were encouraged to increase their medication. The median follow-up for the

primary endpoint was 21 months.

“In men, the lowest hazards of death or hospitalization for heart failure occurred at 100% of the recommended dose of ACE inhibitors or ARBs and beta-blockers, but women showed about 30% lower risk at only 50% of the recommended doses, with no further decrease in risk at higher dose levels,” the researchers wrote. “These sex differences were still present after adjusting for clinical covariates, including age and body surface area.”

The researchers analyzed an Asian registry (3,539 men, 961 women) as a comparison and found the identical numbers.

“Our study provides evidence supporting the hypothesis that women with HFrEF might have the best outcomes with lower doses of ACE inhibitors or ARBs and beta-blockers than do men, and lower doses than recommended in international guidelines for heart failure,” they wrote. However, they added that it was not likely that sex-specific studies analyzing doses would be performed.

In an accompanying editorial,

Heather P. Whitley, PharmD, and Warren D. Smith, PharmD, noted that clinical research has often failed to take gender differences into account. They wrote that the study – the first of its kind – was well executed and raises important questions, but the analysis did not take into account the prevalence of adverse effects or the serum concentrations of the various medications. Although those limitations weaken the findings, the study still offers evidence that gender-based, drug-dose guidelines deserve consideration, wrote Dr. Whitley, of Auburn (Ala.) University, and Dr. Smith, of Baptist Health System, Montgomery, Ala. (*Lancet*. 2019 Aug 22. doi: 10.1016/S0140-6736[19]31812-4).

The study was funded by the European Commission. Several study authors reported various disclosures. Dr. Whitley and Dr. Smith reported no conflicts of interest.

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SOURCE: Santema BT et al. *Lancet*. 2019 Aug 22. doi: 10.1016/S0140-6736(19)31792-1.

Visceral adiposity tied to higher risk of masked hypertension

BY M. ALEXANDER OTTO

MDedge News

NEW ORLEANS – Visceral adiposity, but not body mass index or total body fat, significantly correlated with elevated 24-hour ambulatory systolic blood pressure, greater systolic variability, and masked hypertension in a study from the University of Pennsylvania, Philadelphia.

Subjects in the highest quartile of visceral fat had a 6.3-fold greater odds of masked hypertension – normal in the office, but high at home – compared with those in the lowest quartile (95% confidence interval, 1.2-33.1).

The study findings suggest that central obesity, in particular, should trigger 24-hour ambulatory blood pressure monitoring (ABPM). “Every obese person should get a 24-hour” ABPM, but “we really need to be pushing [it] in people who have central adiposity. These are the patients ... we really need to focus on” because of the risk of masked hypertension, a “ticking time bomb” that greatly increases the risk of cardiovascular events, said lead investigator Jordana B. Cohen, MD, an assistant professor of medicine at the university.

The study also helps explain why body mass index hasn’t been consistently linked to masked hypertension in previous studies; some studies likely included subjects with high BMIs but not central obesity.

Waist circumference, a marker of visceral adiposity, also correlated with elevated 24-hour sys-

tolic pressure and greater variability, but a trend for masked hypertension was not statistically significant, Dr. Cohen reported at the joint scientific sessions of the American Heart Association (AHA) Council on Hypertension, AHA Council on Kidney in Cardiovascular Disease, and American Society of Hypertension.



Dr. Cohen

It’s long been known that visceral fat – fat around the abdominal organs – is metabolically active and associated with greater cardiovascular risk, but its relationship to blood pressure hadn’t been well described, so Dr. Cohen and her team decided to take a look. They ran whole-body dual-energy x-ray absorptiometry scans on 96 hypertensive adults on a stable dose of one anti-hypertensive drug for at least 2 months and correlated the findings with ABPM. Subjects were an average of 58 years old, almost 60% were women, almost half were black, and 54% were obese, with BMIs of at least 30 kg/m².

After adjustment for age, sex, race, and anti-hypertensive class, the team found a significant, linear correlation between visceral fat and mean 24-hour systolic blood pressure. Patients with a visceral adiposity of about 0.1 kg/m², for instance, had a mean pressure of around 130 mm Hg, compared with patients with more than 0.6 kg/m², who had a mean of almost 150 mm Hg.

Findings were similar for waist circumference over a range of 70-150 cm.

The correlations were weak ($r = 0.3$), but Dr. Cohen said they might improve with ongoing enrollment. Both measures also correlated with systolic variability.

Overall, the highest quartiles of waist circumference and visceral adiposity correlated with the highest mean systolic pressures and greatest variability, compared with the lowest quartiles. Visceral adiposity was the only measure significantly linked with masked hypertension. Trends in those directions for increasing BMI and total body fat mass were not statistically significant.

Mean BMI in the study was 31.7 kg/m², and mean waist circumference was 104 cm. Mean 24-hour systolic blood pressure was 135 mm Hg and mean 24-hour systolic variability was 13 mm Hg. Almost 30% of the subjects had masked hypertension. Drug classes included beta-blockers, calcium channel blockers, diuretics, ACE inhibitors, and angiotensin receptor blockers.

Dr. Cohen plans to investigate drug response versus visceral adiposity once the recruitment goal of 150 subjects is reached.

There was no external funding, and the investigators reported that they didn’t have any relevant disclosures.

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SOURCE: Cohen JB et al. *Joint Hypertension* 2019, Abstract P2052.

Daily polypill lowered CV risk in underserved community

BY JAKE REMALY

MDedge News

A daily polypill regimen improved cardiovascular risk factors in a socioeconomically vulnerable minority population, in a randomized controlled trial.

Patients at a federally qualified community health center in Alabama who received treatment with a combination pill for 1 year had greater reductions in systolic blood pressure and LDL cholesterol than did patients who received usual care, according to results published online on Sept. 19 in the *New England Journal of Medicine*.

“The simplicity and low cost of the polypill regimen make this approach attractive” when barriers such as lack of income, underinsurance, and difficulty attending clinic visits are common, said first author Daniel Muñoz, MD, of Vanderbilt University in Nashville, Tenn., and coinvestigators. The investigators obtained the pills at a cost of \$26 per month per participant.

Common risk factors with low treatment rates

People with low socioeconomic status and those who are nonwhite have high cardiovascular mortality, and the southeastern United States and rural areas have disproportionately high levels of cardiovascular

disease burden, according to the investigators. The rates at which people with low socioeconomic status receive treatment for hypertension and hypercholesterolemia – leading cardiovascular disease risk factors –

“Although the precision approach has clear virtues, a broader approach may benefit patients who face barriers to accessing the full advantages of precision medicine.”

“are strikingly low,” Dr. Muñoz and colleagues said.

To assess the effectiveness of a polypill-based strategy in an underserved population with low socioeconomic status, the researchers conducted the randomized trial.

They enrolled 303 adults without cardiovascular disease, and 148 of the patients were randomized to receive the polypill, which contained generic versions of atorvastatin (10 mg), amlodipine (2.5 mg), losartan (25 mg), and hydrochlorothiazide (12.5 mg). The remaining 155 patients received usual care. All participants scheduled 2-month and 12-month follow-up visits.

The participants had an average age of 56 years, 60% were women,

and more than 95% were black. More than 70% had an annual household income of less than \$15,000. Baseline characteristics of the treatment groups did not significantly differ.

At baseline, the average BP was 140/83 mm Hg, and the average LDL cholesterol level was 113 mg/dL.

In all, 91% of the participants completed the 12-month trial visit. Average systolic BP decreased by 9 mm Hg in the group that received the polypill, compared with 2 mm Hg in the group that received usual care. Average LDL cholesterol level decreased by 15 mg/dL in the polypill group, versus 4 mg/dL in the usual-care group.

Changes in other medications

Clinicians discontinued or reduced doses of other antihypertensive or lipid-lowering medications in 44% of the patients in the polypill group and none in the usual-care group. Clinicians escalated therapy in 2% of the participants in the polypill group and in 10% of the usual-care group.

Side effects in participants who received the polypill included a 1% incidence of myalgias and a 1% incidence of hypotension or light-headedness. Liver function test results were normal.

Five serious adverse events that occurred during the trial – two in the polypill group and three in the

usual-care group – were judged to be unrelated to the trial by a data and safety monitoring board.

The authors noted that limitations of the trial include its open-label design and that it was conducted at a single center.

“It is important to emphasize that use of the polypill does not preclude individualized, add-on therapies for residual elevations in blood-pressure or cholesterol levels, as judged by a patient’s physician,” said Dr. Muñoz and colleagues. “We recognize that a ‘one size fits all’ approach to cardiovascular disease prevention runs counter to current trends in precision medicine, in which clinical, genomic, and lifestyle factors are used for the development of individualized treatment strategies. Although the precision approach has clear virtues, a broader approach may benefit patients who face barriers to accessing the full advantages of precision medicine.”

The study was supported by grants from the American Heart Association Strategically Focused Prevention Research Network and the National Institutes of Health. One author disclosed personal fees from Novartis outside the study.

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SOURCE: Muñoz D et al. *N Engl J Med*. 2019 Sep 18;381(12):1114-23. doi: 10.1056/NEJMoa1815359.

Drug abuse–linked infective endocarditis spiking in U.S.

BY JENNIE SMITH

MDedge News

Hospitalizations for infective endocarditis associated with drug abuse doubled in the United States from 2002 to 2016, in a trend investigators call “alarming,” and link to a concurrent rise in opioid abuse.

Patients tend to be younger, poorer white males, according to findings published online in the *Journal of the American Heart Association*.

For their research, Amer N. Kadri, MD, of the Cleveland Clinic and colleagues looked at records for nearly a million hospitalizations for infective endocarditis (IE) in the National Inpatient Sample registry. All U.S. regions saw increases in drug abuse–linked cases of IE as a share of IE hospitalizations. Incidence of drug abuse–associated IC rose from 48 cases/100,000 population in 2002 to 79/100,000 in 2016. The Midwest saw the highest rate of change, with an annual percent increase of 4.9%.

While most IE hospitalizations in the study cohort were of white men (including 68% for drug-linked cases), the drug abuse–related cases were



younger (median age, 38 vs. 70 years for non-drug-related IE), and more likely male (55.5% vs. 50%). About 45% of the drug-related cases were in people receiving Medicaid, and 42% were in the lowest quartile of median household income.

The drug abuse cases had fewer renal and cardiovascular comorbidities, compared with the nondrug cases, but were significantly more likely to present with HIV, hepatitis C, alcohol abuse, and liver disease. Inpatient mortality was lower

among the drug-linked cases – 6% vs. 9% – but the drug cases saw significantly more cardiac or valve surgeries, longer hospital stays, and higher costs.

“Hospitalizations for IE have been increasing side by side with the opioid epidemic,” the investigators wrote in their analysis. “The opioid crisis has reached epidemic levels, and now drug overdoses have been the leading cause of injury-related death in the U.S. Heroin deaths had remained relatively low from 1999 until 2010 whereas it then increased threefold from 2010–2015.” The analysis showed a rise in drug abuse–associated IE “that corresponds to this general period.” The findings argue, the investigators said, for better treatment for opioid addiction after hospitalization and greater efforts to make drug rehabilitation available after discharge. The researchers described as a limitation of their study the use of billing codes that changed late in the study period, increasing detection of drug abuse cases after 2015. They reported no outside funding or conflicts of interest.

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SOURCE: Kadri AN et al. *J Am Heart Assoc*. 2019;8:e012969.

High-flow nasal cannula: Higher limit cut down on bronchiolitis ICU transfers

BY M. ALEXANDER OTTO

MDedge News

SEATTLE – ICU transfers for acute bronchiolitis dropped 63% at Johns Hopkins All Children's Hospital in St. Petersburg, Fla., after the high-flow nasal cannula limit on the floor was raised from 6 L/min to 12 L/min, and treatment was started in the emergency department, according to a presentation at Pediatric Hospital Medicine.

A year before the change was made in April 2018, there were 17 transfers among 249 bronchiolitis patients treated on the floor, a transfer rate of 6.8%. In the year after the change, there were 8 among 319 patients, a transfer rate of 2.5%. Raising the limit to 12 L/min prevented an estimated 14 transfers, for a total savings of almost \$250,000, said pediatric hospitalist and assistant professor Shaila Siraj, MD.

The change was made after Dr. Siraj and her colleagues noticed that, when children topped out at



Dr. Shaila Siraj



Dr. Anthony Sochet

“You have to ask what floor resources you have, what’s your ability to escalate when you need to. Use data from your own institution to guide where you pick your cutoffs. Adequate staffing is really about respiratory [therapist]/nursing ratios, not the physicians,” said Dr. Sochet.

6 L, they sometimes only needed a slightly higher flow rate in the ICU, maybe 8 L or 10 L, for a short while

before they came back to the floor. Given the safety of high-flow nasal cannula (HFNC), the ICU transfer often seemed like a waste of time and resources.

“As hospitalists, we felt we could safely take care of these patients,” Dr. Siraj said.

So she and her colleague pediatric critical care specialist Anthony Sochet, MD, also an assistant professor of pediatrics, reviewed over a year’s worth of data at All Children’s. They found that 12 L/min – roughly 1.5 L/kg/min – was the cutoff that best discriminated between patients who needed intubation and those who did not, “so that’s what we chose,” Dr. Sochet said.

For simplicity, they broke limits down by age: a maximum flow rate of 8 L/min for children up to 6 months old; 10 L for children aged 6-12 months; and up to 12 L/min for children age 12-24 months. The fraction of inspired oxygen remained the same at 50%. Children were started at maximum flows, then weaned down as they improved. Respiratory assessments were made at least every 4 hours.

The changes were part of a larger revision of the hospital’s pathway for uncomplicated bronchiolitis in children up to 2 years old; it was a joint effort involving nurses, respiratory therapists, and pediatric hospitalists, and ED and ICU teams.

Early initiation in the ED was “probably one of the most important” changes; it kept children from wearing out as they struggled to breathe. Kids often start to improve right away, but when they don’t after 30-60 minutes, it’s an indication that they should probably be triaged to the ICU for possible intubation, Dr. Siraj said.

Dr. Sochet was careful to note that institutions have to assess their own situations before taking similar steps. “Not everyone has a tertiary care ICU staffed 24 and 7,” he said.

“You have to ask what floor resources you have, what’s your ability to escalate when you need to. Use data from your own institution to guide where you pick your cutoffs. Adequate staffing is really about respiratory [therapist]/nursing ratios, not the physicians,” he said.

In addition, “in an otherwise healthy child that just has [HFNC] for bronchiolitis, there is absolutely no reason why you should be withholding feeds.” Fed children will feel better and do better, he said.

The presenters had no disclosures. aotto@mdedge.com

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Susan Millard, MD, FCCP, comments: Quite a bit more research needs to be done regarding use of high-flow nasal cannula (HFNC) therapy for bronchiolitis patients. In addition, at the end of the article, the researcher comments on feeding patients on high-flow nasal cannula therapy. I want to see more research in this area. My perspective is that we receive consults on babies who are on the floor, unable to wean from HFNC, and the first thing we recommend is to stop feeding those babies orally. Is the airway being safely protected without micro-aspiration when on HFNC for acute respiratory failure?

Parent education ups pediatric flu vaccination rate

BY CHRISTOPHER PALMER
MDedge News

A brief educational handout about influenza and vaccination prior to seeing a health care provider increased pediatric vaccination rates by the season's end, according to a randomized clinical trial published in *Pediatrics*.

Vanessa P. Scott, MD, MS, of Columbia University, New York, and colleagues randomized 400 parent-child dyads into any of three



Dzurag/Getty Images

arms: receiving a handout based on national data, receiving a handout based on local data, or receiving usual care. This convenience sample was drawn from two pediatric clinics in New York between August 2016 and March 2017.

After adjustment for parents' education level, the trial found that parents who received either handout were significantly more likely than were those receiving usual care to vaccinate their children by the end of season (75% and 65%, respectively; adjusted odds ratio, 1.68; 95% confidence interval, 1.06-2.67), but the effects of any intervention versus those of usual care on vaccination on day of visit were not statistically significant (59% vs. 53%; aOR, 1.36; 95% CI, 0.89-2.09). The researchers had hoped that using a targeted approach based on local data would increase vaccine receipt, but that was not seen in the results.

They did find that, across all three arms in the trial, baseline parental intent to vaccinate (likely versus unlikely) was associated with vaccination rates: Both vaccination on clinic visit day (70% vs. 22%; aOR, 8.38; 95% CI, 4.85-14.34) and vaccination by end of season (87% vs. 29%; aOR, 18.26; 95% CI, 9.94-33.52) were affected.

Strengths of the study included the randomized, controlled design and assessment of baseline factors,

such as intention to vaccinate, to reduce confounding effects. Limitations included use of a convenience sample, which could have introduced selection bias.

One author was an unremuner-

ated coinvestigator of an unrelated trial that received an investigator-initiated grant from the Pfizer Medical Education Group. Two authors were funded by other grants, but no potential conflicts of interests

to disclose were indicated by any of the authors in this study.

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SOURCE: Scott VP et al. *Pediatrics*. 2019. doi: 10.1542/peds.2018-2580.

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Study shows how to predict CF bronchiectasis in children early in life

BY MICHELE G. SULLIVAN

MDedge News

Among preschool children with cystic fibrosis, airway disease as measured by the Perth-Rotterdam Annotated Grid Morphometric Analysis for CF (PRAGMA-CF) accurately predicts bronchiectasis in grade school, reported Nynke R. Bouma, BSc, and colleagues.

“Even though bronchiectasis is present in 60% to 80% of children with CF in school age, the extent and severity of bronchiectasis in preschool children are generally lower. ... however, diffuse airway abnormalities such as airway wall thickening and mucus plugging are observed in many preschool children. It is hypothesized that these preschool airway changes reflect diffuse airway disease that eventually will result in bronchiectasis in school age,” they noted.

The PRAGMA-CF image scoring system can measure airway disease and can also be used to monitor disease progression, noted Ms. Bouma of Sophia Children’s Hospital, Rotterdam, and colleagues. The study was published in *Pediatric Pulmonology*. PRAGMA-CF is a composite score of airway wall thickening, mucus plugging, and

bronchiectasis as percent disease (%disease). “In preschool children, %disease measured by PRAGMA-CF on chest CT allows quantification of early clinically relevant morphological features of CF airway disease and it is associated with later school-age bronchiectasis,” the team wrote. “These findings support the use of %disease as a clinically relevant outcome measure in early CF lung disease.”

The team conducted a prospective cohort study of 61 children (mean age 4 years) with cystic fibrosis, following them for a mean of 5 years. A total of 122 CT scans were available from this group, in addition to spirometry data and cystic fibrosis quality of life scores.

From preschool age to school age, the %disease on PRAGMA-CF increased significantly, from a mean of 0.7% to 1.73%. Scores on another composite measuring tool (%MUPAT, a composite score of airway wall thickening and mucus plugging) went from 0.46 to 0.58 – not a significant difference. A multivariate analysis corrected for age in each school group and the type of scanner used to acquire the images. That analysis determined that each 1% increase in %disease at preschool age resulted in an increase of 1.18% of bronchiectasis at school age.

A cross-sectional analysis of the group at school age found significant associations between the %disease and percent of forced expiratory volume and the cystic fibrosis quality of life score.

At least one pulmonary exacerbation requiring intravenous antibiotics occurred in 19 of the patients. However, the investigators didn’t find any significant interactions between the %disease in preschool and these exacerbations.

“These findings are in line with previous studies in school-aged children that showed that mucus plugging is associated with inflammation and airway wall thickening, and that these are thought to be risk factors for later bronchiectasis,” they concluded. “We suggest that %disease and %MUPAT could be used as a clinically relevant outcome measure in clinical studies in preschool patients with cystic fibrosis, as these measures predict later bronchiectasis. Percent disease may be preferred as it captures all the principal features of CF airways disease including bronchiectasis.”

Ms. Bouma had no financial disclosures.

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SOURCE: Bouma NR et al. *Pediatr Pulmonol*. 2019 Sep 9. doi: 10.1002/ppul.24498

Case study: CPAP kept infants with bronchiolitis out of ICU

BY M. ALEXANDER OTTO

MDedge News

SEATTLE – Rady Children’s Hospital in San Diego has been doing continuous positive airway pressure (CPAP) for infants with bronchiolitis on the general pediatrics floors safely and with no problems for nearly 20 years, according to a presentation at Pediatric Hospital Medicine meeting.

It’s newsworthy because “very, very few” hospitals do bronchiolitis CPAP outside of the ICU. “The perception is that there are complications, and you might miss kids that are really sick if you keep them on the floor.” However, “we have been doing it safely for so long that no one thinks twice about it,” said Christiane Lenzen, MD, a pediatric hospitalist at Rady and an assistant clinical professor of pediatrics at the University of California, San Diego.

It doesn’t matter if children have congenital heart disease, chronic lung disease, or other problems, she said, “if they are stable enough for the floor, we will see if it’s okay.”

Rady’s hand was forced on the issue because it has a large catchment area but limited ICU beds, so for practical reasons and within certain limits, CPAP moved to the floors. One of Dr.

Lenzen’s colleagues noted that, as long as there’s nurse and respiratory leadership buy in, “it’s actually quite easy to pull off in a very safe manner.”

Rady has a significant advantage over community hospitals and other places considering the approach, because it has onsite pediatric ICU services for when things head south. Over the past 3 or so years, 52% of



Dr. Lenzen

the children the pediatric hospital medicine service started on CPAP (168/324) had to be transferred to the ICU; 17% were ultimately intubated.

Many of those transfers were caused by comorbidities, not CPAP failure, but other times children needed greater respiratory support; in general, the floor CPAP limit is 6 cm H₂O and a fraction of inspired oxygen of 50%. Also, sometimes children needed to be sedated for CPAP, which isn’t done on the floor.

With the 52% transfer rate, “I would worry about patients who are sick enough to need CPAP staying”

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: It would take a unique and detailed hospital care map to safely manage acute CPAP on the floor. More research is imperative.

in a hospital without quick access to ICU services, Dr. Lenzen said at the meeting sponsored by the Society of Hospital Medicine, the American Academy of Pediatrics, and the Academic Pediatric Association.

Even so, among 324 children who at least initially were treated with CPAP on the floor – out of 2,424 admitted to the pediatric hospital medicine service with bronchiolitis – there hasn’t been a single pneumothorax, aspiration event, or CPAP equipment-related injury, she said.

CPAP on the floor has several benefits. ICU resources are conserved, patient handoffs and the work of transfers into and out of the ICU are avoided, families don’t have to get used to a new treatment team, and infants aren’t subjected to the jarring ICU environment.

For it to work, though, staff “really need to be on top of this,” and “it

needs to be very tightly controlled” with order sets and other measures, the presenters said. There’s regular training at Rady for nurses, respiratory therapists, and hospitalists on CPAP equipment, airway management, monitoring, troubleshooting, and other essentials.

Almost all children on the pediatric floors have a trial of high-flow nasal cannula with an upper limit of 8 L/min. If the Respiratory Assessment Score hasn’t improved in an hour, CPAP is considered. If a child is admitted with a score above 10 and they seem to be worsening, they go straight to CPAP.

Children alternate between nasal prongs and nasal masks to prevent pressure necrosis, and are kept nil per os while on CPAP. They are on continual pulse oximetry and cardiorespiratory monitoring. Vital signs and respiratory scores are checked frequently, more so for children who are struggling.

The patient-to-nurse ratio drops from the usual 4:1 to 3:1 when a child goes on CPAP, and to 2:1 if necessary. Traveling nurses aren’t allowed to take CPAP cases.

The presenters didn’t report any disclosures.

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Guideline: Blood CO₂ can be used to screen for OHS

BY JENNIE SMITH

MDedge News

A blood test for elevated carbon dioxide may be used in screening adults for obesity hypoventilation syndrome, according to new guidelines.

Obese adults with sleep-disordered breathing and increased blood carbon dioxide levels during the day are likely to have obesity hypoventilation syndrome (OHS), a result of shallow or slow breathing that can lead to respiratory failure, heart failure, pulmonary hypertension, and death. Pulmonologists and sleep specialists may be the first to see and diagnose patients with OHS in the outpatient setting, while other cases are diagnosed in the hospital when patients present with hypercapnic respiratory failure.

Screening for OHS usually involves measuring arterial blood gases, which is not standard practice in outpatient clinics. Patients often

remain undiagnosed and untreated until late in the course of the disease, according to the American Thoracic Society, which in August published a new diagnosis and management guideline aiming to boost early diagnosis and reduce variability in treatment (*Am J Respir Crit Care Med.* 2019;200:3,e6-e24).

The guideline authors, led by Babak Mokhlesi, MD, of the University of Chicago, recommend a simpler screening method – measuring serum bicarbonate only – to rule out OHS in obese patients with nighttime breathing problems.

Serum bicarbonate should be measured in obese patients with sleep-disordered breathing and a low likelihood of OHS, Dr. Mokhlesi and colleagues recommend in the guideline. If serum bicarbonate is below 27 mmol/L, it is not necessary to conduct further testing as the patient is unlikely to have OHS.

In patients whose serum bicarbonate is higher than 27 mmol/L,

or who are strongly suspected of having OHS at presentation because of severe obesity or other symptoms, arterial blood gases should be measured and a sleep study conducted. The guideline authors said that there is insufficient evidence to recommend that pulse oximetry be used in the diagnostic pathway for OHS.

First-line treatment for stable, ambulatory patients with OHS should be positive airway pressure during sleep, rather than noninvasive ventilation, Dr. Mokhlesi and colleagues concluded. For patients with comorbid obstructive sleep apnea – as many as 70% of OHS patients also have OSA – the first-line treatment should be continuous positive airway pressure (CPAP) at night, the guideline states.

Patients hospitalized with respiratory failure and suspected of having OHS should be discharged with noninvasive ventilation until diagnostic procedures can be performed, along with PAP titration in a sleep lab.

In patients initially treated with CPAP who remain symptomatic or whose blood carbon dioxide does not improve, noninvasive ventilation can be tried, the guidelines say. Finally, patients diagnosed with OHS should be guided to weight-loss interventions with the aim of reducing body weight by 25%-30%. This can include referral for bariatric surgery in patients without contraindications.

Dr. Mokhlesi and colleagues acknowledged that all of the recommendations contained in the guideline are classed as “conditional,” based on the quality of evidence assessed.

The American Thoracic Society funded the study. Dr. Mokhlesi and 7 coauthors disclosed financial conflicts of interest, while an additional 13 coauthors had none. Disclosures can be found on the AJRCCM website.

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SOURCE: Mokhlesi B et al. *Am J Respir Crit Care Med.* 2019;200:3,e6-24.

Childhood behavioral issues may signal adult insomnia risk

BY CHRISTOPHER PALMER

MDedge News

The odds of adulthood insomnia are significantly higher among those with childhood behavioral problems, according to research published in *JAMA Network Open*.

Yohannes Adama Melaku, MPH, PhD, of the Adelaide (Australia) Institute for Sleep Health at Flinders University and coauthors drew data from the 1970 UK Birth Cohort Study. This study followed an initial cohort of 16,571 babies who were born during a single week, with follow-up at ages 5, 10, 16, 26, 30, 38, 42, and 46 years. For the purposes of this study, the investigators looked at participants who, at 42 years of age, were alive and not lost to follow-up and who responded to an invitation to be interviewed; the sample sizes in the analysis were 8,050 participants aged 5 years, 9,090 participants aged 10 years, 9,653 participants aged 16 years, and 9,841 participants aged 42 years.

Behavior was measured at ages 5 years and 16 years using the Rutter Behavioral Scale (RBS) and at age 10 years using a visual analog scale, and insomnia symptoms were assessed through interviewing participants in adulthood about duration of sleep, difficulty initiating and maintaining sleep, and not feeling rested on waking. Participants were organized into normal behavior (less than or equal to 80th percentile on RBS), moderate behavioral problems (greater than the 80th percentile but less than or equal to the 95th percentile), and severe behavioral problems (above 95th percentile). The investigators then devised two models for their analysis: Model 1 adjusted



klebercordeiro/Getty Images

for sex, parent's social class and educational level, marital status, educational status, and social class, and model 2 adjusted for physical activity level and body mass index trajectory (from 10 to 42 years), perceived health status, and number of noncommunicable diseases, although this latter model yielded fewer statistically significant results in some analyses.

Odds for difficulty initiating or maintaining sleep as an adult was increased among participants with severe behavioral problems at age 5 years in model 1 (adjusted odds ratio, 1.50; 95%

confidence interval, 1.14-1.96; $P = .004$), as well as for those with severe problems at 10 years (aOR, 1.30; 95% CI, 1.14-1.63; $P = .001$), and at 16 years (aOR, 2.17; 95% CI, 1.59-2.91; P less than .001). The aORs also were higher individually for difficulty initiating sleep and for difficulty maintaining sleep in all age groups.

The association with adulthood insomnia was stronger in participants with externalizing behavioral problems such as lying, bullying, having restlessness, and fighting than it was in those with internalizing behavioral problems such as worry, fearfulness, and solitariness.

“Although early sleep problems should be identified, we should additionally identify children with moderate to severe behavioral problems that persist throughout childhood as potential beneficiaries of early intervention with a sleep health focus,” the authors wrote.

One of the study's limitations was a lack of standardized insomnia measures in the cohort study; however, the researchers suggested that the symptoms included reflect those of standardized measures and diagnostic criteria.

“This study is the first, to our knowledge, to suggest an unfavorable association of early-life behavioral problems with adulthood sleep health, underlining the importance of treating behavioral problems in children and addressing insomnia from a life-course perspective,” they concluded.

No study sponsor was identified. The authors reported no relevant financial disclosures.

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SOURCE: Melaku YA et al. *JAMA Netw Open.* 2019 Sep 6. doi: 10.1001/jamanetworkopen.2019.10861.

Less CPAP time linked to exacerbation in COPD/OSA overlap syndrome

BY JAKE REMALY

MDedge News

Among patients with chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA), lung function and continuous positive airway pressure (CPAP) use are independent predictors of COPD exacerbations and all-cause mortality, according to a retrospective cohort study.

“These factors should be taken into account when considering the management and prognosis of these patients,” the researchers said in the *Clinical Respiratory Journal*.

Prior studies have found that patients with COPD and OSA – that is, with overlap syndrome – “have a substantially greater risk of morbid-

ity and mortality, compared to those with either COPD or OSA alone,” said Philippe E. Jaoude, MD, and Ali A. El Solh, MD, both of the Veterans Affairs Western New York Healthcare System in Buffalo.

To identify factors associated with COPD exacerbation and all-cause mortality in patients with overlap syndrome, Dr. Jaoude and Dr. El Solh reviewed the electronic health records of patients with simultaneous COPD and OSA. They compared patients with overlap syndrome who had an acute exacerbation of COPD during a 42-month period with a control group of patients with overlap syndrome who did not have exacerbations during

that time. Patients with exacerbations and controls were matched 1:1 by age

“Multivariate logistic regression analysis identified the independent risk factors associated with COPD exacerbations as active smoking, worse airflow limitation, and lower CPAP utilization.”

and body mass index.

Eligible patients were aged 42-90 years, had objectively confirmed COPD, and had documented OSA by in-laboratory polysomnography (that is, at least five obstructive apneas and hypopneas per hour). The investigators defined a COPD exacerbation as a sustained worsening of a patient’s

respiratory condition that warranted additional treatment.

Of 225 eligible patients, 92 had at least one COPD exacerbation between March 2014 and September 2017. Patients with COPD exacerbation and controls had a mean age of about 68 years. The group of patients with exacerbation had a higher percentage of active smokers (21% vs. 9%) and had

poorer lung function (mean forced expiratory volume in 1 second percent predicted: 55.2% vs. 64.5%).

“Although the rate of CPAP adherence between the two groups was not significantly different, the average time of CPAP use was significantly higher in patients with no recorded exacerbation,” the researchers reported.

In all, 146 patients (79.4%) survived, and 38 patients (20.6%) died during the study period. The crude mortality rate was significantly higher in the group with COPD exacerbations (14% vs. 7%).

“Multivariate logistic regression analysis identified the independent risk factors associated with COPD exacerbations as active smoking, worse airflow limitation, and lower CPAP utilization,” they said. “As for all-cause mortality, a higher burden of comorbidities, worse airflow limitation, and lower time of CPAP use were independently associated with poor outcome.” The researchers noted that they cannot rule out the possibility that patients who were adherent to CPAP were systematically different from those who were not. The authors declared no conflicts.

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SOURCE: Jaoude P et al. *Clin Respir J*. 2019 Aug 22. doi: 10.1111/crj.13079.

VIEW ON THE NEWS

Octavian C. Ioachimescu, MD, FCCP, comments: In 1985, this comorbid association of COPD and OSA was named by David Flenley the “overlap syndrome” (*Clin Chest Med*. 1985;6:651-61). He posited that the COPD-OSA association had more deleterious effects than either disorder alone. Indeed, we learned over the years that the overlap syndrome presents with worse nocturnal hypoxemia and hypercapnia, more disturbed sleep, more frequent and more severe cardiac arrhythmias, daytime pulmonary hypertension, and higher mortality than either condition. Several (nonrandomized) studies showed that Positive Airway Pressure (PAP) therapy could mitigate the outcome differences noted previously between COPD and overlap syndrome. In the recent study published by Jaoude and El Solh (*Clin Respir J*. 2019), the authors found that lung function and PAP use were independent predictors of all-cause mortality and COPD exacerbations. While this was a retrospective analysis, the study reinforces the concept that the emerging phenotype of the overlap

syndrome may delineate a patient category with much higher morbidity and mortality risks than the ones represented by the mere additive effects of these (and other) comorbidities. Perhaps not surprisingly, patients without COPD exacerbations had longer average time of PAP usage, while lower comorbid burden, better lung function, and longer use of PAP were correlates of better survival in this cohort. Appropriately, the authors indicate that the PAP usage category (long vs short use time) may be in fact a surrogate sign of totally different patient populations. As such, subjects more adherent to the proposed therapeutic plans may intrinsically have better motivation, superior follow-up care, longer PAP time, and improved overall outcomes, a dilemma unfortunately not easily solved in observational studies. Nevertheless, this analysis reinforces the previous signals from the literature on the potential benefits of PAP use in COPD-OSA overlap syndrome.



FDA approves Wakix for excessive daytime sleepiness

BY CHRISTOPHER PALMER

MDedge News

The Food and Drug Administration has approved pitolisant (Wakix) for excessive daytime sleepiness among patients with narcolepsy, according to a release from the drug’s developer.

Approval of this once-daily, selective histamine 3-receptor antagonist/inverse agonist was based on a pair of multicenter, randomized, double-blind, placebo-controlled studies

that included a total of 261 patients. Patients in both studies experienced statistically significant improvements in excessive daytime sleepiness according to Epworth Sleepiness Scale scores.

Rates of adverse events at or greater than 5% and more than double that of placebo included insomnia (6%), nausea (6%), and anxiety (5%). Patients with severe liver disease should not use pitolisant. Pitolisant



has not been evaluated in patients under 18 years of age, and patients who are pregnant or planning to become pregnant are encouraged to enroll in a pregnancy exposure registry.

Jeffrey Dayno, MD, chief medical officer of the drug maker, Harmony Biosciences, stated, “Wakix is the only non-scheduled treatment option approved for adult patients with narcolepsy, and it offers an important benefit/risk profile to address the unmet medical need that exists in people living with narcolepsy.”

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Vitamin C infusion falls short for sepsis and ARDS

BY HEIDI SPLETE

MDedge News

Vitamin C infusion did not improve outcomes related to organ failure, inflammation, or vascular injury for patients with sepsis and acute respiratory distress syndrome, based on data from 167 adults.

“Previous research found that vitamin C attenuates systemic inflammation, corrects sepsis-induced coagulopathy, and attenuates vascular injury,” wrote Alpha A. Fowler III, MD, of Virginia Commonwealth University, Richmond, and colleagues.

To examine the impact of vitamin C infusion on patients with sepsis and acute respiratory distress syndrome (ARDS), the researchers designed the CITRIS-ALI trial, a randomized, double-blind, placebo-controlled study conducted at 7 medical intensive care units in the United States.

In the study, published in JAMA, the researchers randomized 167 adults with sepsis and ARDS to receive high-dose intravenous vitamin C (50 mg/kg in 5% dextrose in water) or placebo (5% dextrose in water only) every 6 hours for 96 hours. The primary outcomes were measures

of organ failure based on changes in the modified Sequential Organ Failure Assessment score (mSOFA), inflammation (based on changes in C-reactive protein), and vascular injury based on thrombomodulin.

Overall, no significant differences appeared between the vitamin C and placebo groups, respectively in the three primary outcome measures:

change in average SOFA score (3-point change vs. a 3.5-point change) at 96 hours; change in C-reactive protein levels (change of 54.1 mcg/mL vs. 46.1 mcg/mL) at 168 hours; and change in thrombomodulin levels (14.5 ng/mL vs. 13.8 ng/mL) at 168 hours.

The average age of the patients was 55 years, and 54% were men.

The researchers also assessed 46 secondary outcomes. Most

of these showed no significant differences between the groups, but 28-day all-cause mortality was significantly lower in the vitamin C group, compared with the placebo group (46.3% vs. 29.8%), the researchers said. Vitamin C also was significantly associated with increased ICU-free days to day 28 and hospital-free days to day 60, compared with placebo.

No significant differences were seen between the groups on 43 other secondary outcomes in-

cluding ventilator-free days and vasopressor use. However, “these findings were based on analyses that did not account for multiple comparisons and therefore must be considered exploratory,” they said.

“The inability of vitamin C to affect C-reactive protein and thrombomodulin levels in this trial possibly resulted from the advanced stages of sepsis that were present before the development of ARDS,” the researchers noted.

The findings were limited by several factors including the variability in the timing of vitamin C administration and the use of a single high dose of vitamin C, they emphasized. However, the results suggest that further research may be needed to determine the potential of vitamin C for improving outcomes in patients with sepsis and ARDS, they said.

The study was supported by the National Heart, Lung, and Blood Institute, National Center for Advancing Translational Sciences, VCU Wright Center for Translational Science Award, VCU Investigational Drug Services, and McGuff Pharmaceuticals, who supplied the vitamin C free of charge. Dr. Fowler disclosed funding from Virginia Polytechnic Institute and State University, Richmond; the NHLBI; and study materials from McGuff Pharmaceuticals.

SOURCE: Fowler AA et al. JAMA. 2019 Oct 1;322:1261-70. doi:10.1001/jama.2019.11825.

“The inability of vitamin C to affect C-reactive protein and thrombomodulin levels in this trial possibly resulted from the advanced stages of sepsis that were present before the development of ARDS.”

Palliative care programs continue growth in U.S. hospitals

BY RICHARD FRANKI

MDedge News

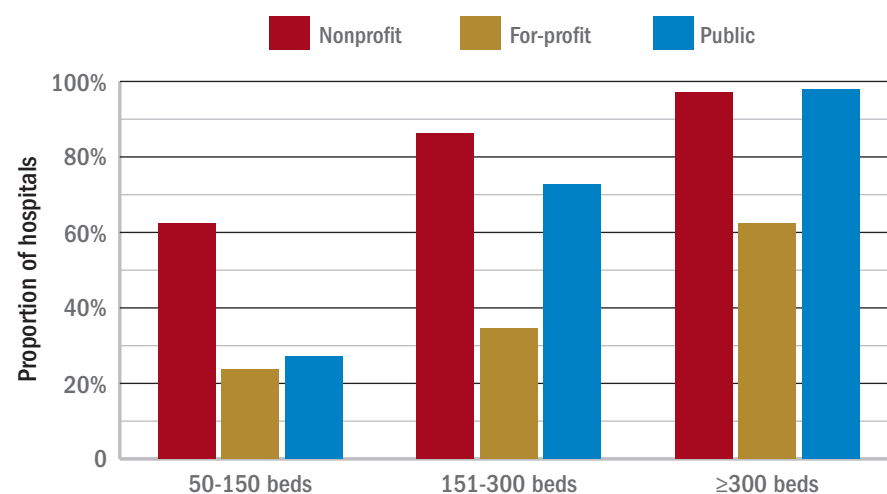
Growth continues among palliative care programs in the United States, although access often depends “more upon accidents of geography than it does upon the needs of patients,” according to the Center to Advance Palliative Care and the National Palliative Care Research Center.

“As is true for many aspects of health care, geography is destiny. Where you live determines your access to the best quality of life and highest quality of care during a serious illness,” said Diane E. Meier, MD, director of the Center to Advance Palliative Care, in a written statement.

In 2019, more than 72% of U.S. hospitals with 50 or more beds have a palliative care team, compared with 67% of hospitals in 2015 and 53% in 2008, the two organizations said in their 2019 report card on palliative care access. What hasn’t changed since 2015, however, is the country’s overall grade, which remains a B.

Delaware, New Hampshire, Rhode

Hospitals with palliative care by size and tax status, 2019



Note: The report card included 1,723 hospitals with a palliative care program and ≥50 beds.

Source: Center to Advance Palliative Care, National Palliative Care Research Center

Island, and Vermont have a palliative care program in all of their hospitals with 50 or more beds and each earned a grade of A (palliative care rate of greater than 80%), along with 17 other states. The lowest-performing states – Alabama, Mississippi, New Mexico, Oklahoma, and Wyoming – all received Ds for having a rate below 40%, the CAPC said.

The urban/rural divide also is prominent in palliative care: “90% of hospitals with palliative care are in urban areas. Only 17% of rural hospitals with fifty or more beds report palliative care programs,” the report said.

Hospital type is another source of disparity. Small, nonprofit hospitals are much more likely to offer access to palliative care than

either for-profit or public facilities of the same size, but the gap closes as size increases, at least between nonprofit and public hospitals. For the largest institutions, the public hospitals pull into the lead, 98% versus 97%, over the nonprofits, with the for-profit facilities well behind at 63%.

“High quality palliative care has been shown to improve patient and family quality of life, improve patients’ and families’ health care experiences, and in certain diseases, prolong life. Palliative care has also been shown to improve hospital efficiency and reduce unnecessary spending,” said R. Sean Morrison, MD, director of the National Palliative Care Research Center.

The report card is based on data from the American Hospital Association’s Annual Survey Database, with additional data from the National Palliative Care Registry and Center to Advance Palliative Care’s Mapping Community Palliative Care initiative. The final sample included 2,409 hospitals with 50 or more beds.

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CDC activates Emergency Operations Center for vaping-injury resources

BY KATIE LENNON

MDedge News

The Centers for Disease Control and Prevention has activated its Emergency Operations Center for the purpose of improving multiple agencies' responses to the current investigation into cases of lung injury associated with vaping. The CDC is fast-tracking Web resources such as up-to-date information concerning ongoing research and discovery as well as channels for reporting cases

The CDC is fast-tracking Web resources such as up-to-date information, recommendations, and reporting channels for public health officials, clinicians, hospitals, and critical care facilities.

and recommendations for clinical management aimed at public health officials, clinicians, hospitals, and critical care facilities.

This move allows the CDC "to provide increased operational support" to CDC staff to meet the evolving challenges of the outbreak of vaping-related injuries and deaths, says a statement from the CDC.

"CDC has made it a priority to find out what is causing this outbreak," noted CDC Director Robert Redfield, MD, in the statement.

The agency "continues to work closely with the U.S. Food and Drug Administration to collect information about recent e-cigarette product use, or vaping, among patients and to test the substances or chemicals within e-cigarette products used by case patients," according to the statement.

The CDC provided email addresses and site addresses for gathering information and communicating about e-cigarettes. Information about the collection of e-cigarettes for possible testing by FDA can be obtained by contacting FDAVapingSampleInquiries@fda.hhs.gov. To communicate with CDC about this public health response, clinicians and health officials can contact LungDiseaseOutbreak@cdc.gov.

More information on the current outbreak related to e-cigarettes is available at https://www.cdc.gov/tobacco/basic_information/e-ciga-

[rettes/severe-lung-disease.html](https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html).

General information on electronic cigarette products, can be found at

www.cdc.gov/e-cigarettes.

Individuals should consider refraining from e-cigarette use while

the cases of lung injury are being investigated, the CDC said.

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Study challenges fluid resuscitation guidelines

BY TED BOSWORTH

MDedge News

Although guideline recommended, treating children in shock with a bolus of saline or

albumin fluid imposes counterproductive effects on respiratory and neurologic function, ultimately increasing risk of death, according to a detailed analysis of available data, including a randomized trial.

Several sets of guidelines for resuscitation of patients in shock have advocated volume expansion with bolus intravenous fluid, but that recommendation was based on expected physiologic benefits,

not a randomized trial. The only randomized trial associated this approach showed increased mortality, and a new analysis of these and other data appears to explain why.

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According to the findings of a study lead by Michael Levin, MD, of the department of medicine at Imperial College London and colleagues, “volume resuscitation is associated with deterioration of respiratory function and neurological function in some patients.” Their study was published in *Lancet*

Respiratory Medicine. The authors stated that saline-induced hyperchloremic acidosis appears to have been “a major contributor” to the observed increase in adverse outcomes.

The key take-home message is that “normal saline and other unbuffered crystalloid solutions should

be avoided in resuscitating seriously ill patients,” according to the authors, who believe the findings might be relevant to adults as well as children.

The controversy about the role of volume expansion for management of shock was ignited by a 2011 trial called FEAST (*N Engl J Med*.

2011;364:2483-95). That trial, which randomized African children with severe febrile illness to a bolus of 20–40 mg of 5% albumin solution, a bolus of 0.9% saline solution, or no bolus, was halted early when 48-hour mortality data showed a lower death rate in the no-bolus group (7.3%) than either the albumin (10.6%) or saline (10.5%) bolus groups.

The FEAST result was unexpected and so contrary to accepted thinking that it prompted widespread debate, including whether findings in the resource-poor area of the world where the FEAST trial was conducted could be extrapolated to centers elsewhere in the world. As an argument for benefit: Fluid resuscitation is known to increase pulse pressure and urinary output. As an argument against benefit: Pulmonary edema is a known complication of bolus fluid replacement.

In an attempt to address and potentially resolve this controversy, data collected in the FEAST trial along with four other sets of data involving volume expansion in critically ill children were evaluated with a focus on changes in cardiovascular, neurological, and respiratory function. Analysis of blood biochemistry and blood oxygen transport were also conducted.

The cardiovascular, respiratory, and neurologic functions were scored on the basis of objective measurements, such as heart rate, respiratory rate, and blood pressure. These measures were evaluated prior to fluid administration and at 1 hour, 4 hours, 8 hours, 24 hours, and 48 hours after fluid administration. Odds ratio (OR) of an adverse outcome were evaluated in the context of each 10-unit change in these scores.

Relative to baseline, there was worsening respiratory and neurological function after fluid administration. Although cardiovascular function improved, hemoglobin concentrations were lower in those who received fluid than in those who did not. Fluid resuscitation was also associated with lower bicarbonate and increased base deficit and chloride at 24 hours.

Regression modeling with physiological variables suggests “that the increased mortality in FEAST can be explained by bolus-induced worsening in respiratory and neurological function, hemodilution, and hyperchloremic acidosis,” according to the authors.

The authors disclosed no conflicts.
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SOURCE: Levin M et al. *Lancet Respir Med*. 2019;7:581-93.

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High mortality rates trail tracheostomy patients

BY HEIDI SPLETE

MDedge News

Long-term outcomes after tracheostomy are generally poor and health care costs are high, especially for older patients, findings of a large retrospective study suggest.

Current outcome prediction tools to support decision making regarding tracheostomies are limited, wrote Anuj B. Mehta, MD, of National Jewish Health in Denver, and colleagues. “This study provides novel and in-depth insight into mortality and health care utilization following tracheostomy not previously described at the population-level.”

In a study published in *Critical Care Medicine*, the researchers reviewed data from 8,343 nonsurgical patients seen in California hospitals from 2012 to 2013 who received a tracheostomy for acute respiratory failure.

Overall, the 1-year mortality rate for patients who had tracheostomies (the primary outcome) was 46.5%, with in-hospital mortality of 18.9% and 30-day mortality of 22.1%. Pneumonia was

the most common diagnosis for patients with respiratory failure (79%) and some had an additional diagnosis, such as severe sepsis (56%).

Patients aged 65 years and older had significantly higher mortality than those under 65 (54.7% vs. 36.5%). The average age of the patients was 65 years; approximately 46% were women and 48% were white. The median survival for adults aged 65 years and older was 175 days, compared with median survival of more than a year for younger patients.

Secondary outcomes included discharge destination, hospital readmission, and health care utilization. A majority (86%) of patients were discharged to a long-term care facility, while 11% were sent home and approximately 3% were discharged to other destinations.

Nearly two-thirds (60%) of patients were readmitted to the hospital within a year of tracheostomy, and readmission was more common among older adults, compared with younger (66% vs. 55%).

In addition, just over one-third of all patients (36%) spent more than 50% of their days alive in the hospital in short-term acute care, and this

rate was significantly higher for patients aged 65 years and older, compared with those under 65 (43% vs. 29%). On average, the total hospital cost for patients who survived the first year after tracheostomy was \$215,369, with no significant difference in average cost among age groups.

The study findings were limited by several factors including the use of data from a single state, possible misclassification of billing codes, and inability to measure quality of life, the researchers noted.

However, “our findings of high mortality, low median survival for older patients, high readmission rates, potentially burdensome cost, and informative outcome trajectories provide significant insight into long-term outcomes following tracheostomy,” they concluded.

Dr. Mehta and several colleagues reported receiving funding from the National Institutes of Health. The researchers disclosed no conflicts.

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SOURCE: Mehta AB et al. *Crit Care Med*. 2019 Aug 8. doi: 10.1097/CCM.0000000000003959.

Hospital-acquired *C. diff.* tied to ‘high-risk’ antibiotic classes

BY MARK S. LESNEY

MDedge News

The use of four antibiotic classes designated “high risk” was

found to be an independent predictor of hospital-acquired *Clostridioides difficile* (CDI), based upon an analysis of microbiologic and pharmacy data from 171 hos-

pitals in the United States.

The high-risk antibiotic classes were second-, third-, and fourth-generation cephalosporins, fluoroquinolones, carbapenems, and lincosamides, according to a report by Ying P. Tabak, PhD, of Becton Dickinson in Franklin Lakes, N.J., and colleagues published in *Infection Control & Hospital Epidemiology*.

Of the 171 study sites, 66 (39%) were teaching hospitals and 105 (61%) were nonteaching hospitals. The high-risk antibiotics most frequently used were cephalosporins (47.9%), fluoroquinolones (31.6%), carbapenems (13.0%), and lincosamides (7.6%). The sites were distributed across various regions of the United States. The hospital-level antibiotic use was measured as days of therapy (DOT) per 1,000 days present (DP).

The study was not able to determine specific links to individual antibiotic classes but to the use of high-risk antibiotics as a whole, except for cephalosporins, which were significantly correlated with hospital-acquired CDI ($r = 0.23$; P less than .01).

The overall correlation of high-risk antibiotic use and hospital-acquired CDI was 0.22 ($P = .003$). Higher correlation was observed in teaching hospitals ($r = 0.38$; $P = .002$) versus nonteaching hospitals ($r = 0.19$; $P = .055$), according to the researchers. The authors attributed this to the possibility of teaching

hospitals dealing with more elderly and sicker patients.

After adjusting for significant confounders, the use of high-risk antibiotics was still independently associated with significant risk for hospital-acquired CDI. “For every 100-day increase of DOT per 1,000 DP in high-risk antibiotic use, there was a 12% increase in [hospital-acquired] CDI (risk ratio, 1.12; 95% [confidence interval], 1.04-1.21; $P = .002$),” according to the authors. This translated to four additional hospital-acquired CDI cases with every 100 DOT increase per 1,000 DP.

“Using a large and current dataset, we found an independent impact of hospital-level high-risk antibiotic use on [hospital-acquired] CDI even after adjusting for confounding factors such as community CDI pressure, proportion of patients aged 65 years or older, average length of stay, and hospital teaching status,” the researchers concluded.

Funding was provided by Nabri-va Therapeutics, an antibiotic development company. Four of the authors are full-time employees of Becton Dickinson, which sells diagnostics for infectious diseases, including CDI, and one author was an employee of Nabri-va Therapeutics.

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SOURCE: Tabak YP et al. *Infect Control Hosp Epidemiol*. 2019 Sep 16. doi: 10.1017/ice.2019.236.

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A quarter of ICU admissions due to substance abuse

BY CALEB RANS

MDedge News

FROM THE JOURNAL CHEST

Nearly a quarter of resources used by the intensive care unit (ICU) are for substance abuse–related admissions, according to results from a retrospective chart review.

The abuse of illicit drugs topped substance abuse–related ICU stays, accounting for 13% of total admissions, which represented 11% of total charges.

“We conducted a study to provide updated data on ICU utilization and costs related to licit and illicit abuse at a large county hospital,” wrote Donald Westerhausen, MD, of Indiana University, Indianapolis, and colleagues. The findings were reported in *Chest*.

The single-center study comprised 594 patients who were admitted for prescription, alcohol, or illicit drug use between May 2017 and October 2017. The team used laboratory

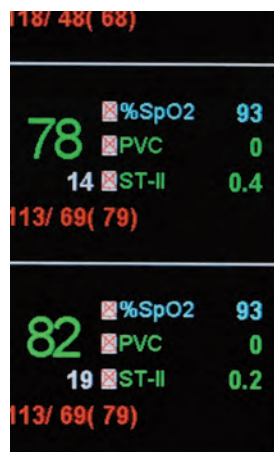
data, in addition to medical history, to define substance abuse–related admissions.

A total of 611 admissions occurred during the 6-month study period. The researchers collected information on patient demographics, hospital charges, insurance coverage, and other clinical parameters.

After analysis, they found that patients admitted for substance abuse were generally younger than were those admitted for other reasons (44 years vs. 59 years; *P* less than .001). In addition, patients were more often male (64% vs. 48%), had greater mortality (14%), and experienced longer hospital stays (median, 6 days).

In total, 25.7% of ICU admissions were related to substance abuse, which comprised 23.1% of charges. In particular, 9.5% and 2.9% of admissions were related to alcohol use and prescription drugs, which represented 7.6% and 4.2% of total charges, respectively.

“Polysubstance abuse was the



Andrei Malov/Thinkstock

most frequent subcategory of illicit and prescription drug admissions,” the researchers wrote.

They acknowledged two limitations of the study: the short duration and single-center design. Future studies should account for seasonal differences in ICU admissions, they noted.

“Identifying and accurately describing the landscape of this cur-

rent health crisis will help us take appropriate action in the future,” they concluded.

No funding sources were reported. The authors did not disclose any conflicts of interest.

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SOURCE: Westerhausen D et al. *Chest*. 2019 Sep 5. doi: 10.1016/j.chest.2019.08.2180.

Procalcitonin can be useful to rule out bacterial infection

BY M. ALEXANDER OTTO

MDedge News

SEATTLE – Procalcitonin, a marker of bacterial infection, rises and peaks sooner than C-reactive protein (CRP), and is especially useful to help rule out invasive bacterial infections in young infants and pediatric community-acquired pneumonia due to typical bacteria, according to a presentation at the Pediatric Hospital Medicine meeting.

It’s “excellent for identifying low-risk patients” and has the potential to decrease lumbar punctures and antibiotic exposure, but “the specificity isn’t great,” so there’s the potential for false positives, said Russell McCulloh, MD, a pediatric infectious disease specialist at the University of Nebraska Medical Center, Omaha.

There was great interest in procalcitonin at the meeting; the presentation room was packed, with a line out the door. It’s used mostly in Europe at this point. Testing is available in many U.S. hospitals, but a large majority of audience members, when polled, said they don’t currently use it in clinical practice, and that it’s not a part of diagnostic algorithms at their institutions.

Levels of procalcitonin, a calcitonin precursor normally produced by the thyroid, are low or undetectable in healthy people, but inflammation, be it from infectious or noninfectious causes, triggers production by parenchymal cells throughout the body.

Levels began to rise as early as 2.5 hours after healthy subjects in one study were injected with bacterial endotoxins, and peaked as early as 6 hours; CRP, in contrast, started to rise after 12 hours, and peaked at 30 hours. Procalcitonin lev-



(From left) Dr. Marie Wang, Dr. Russell McCulloh, and Dr. Nivedita Srinivas spoke in Seattle.

els also seem to correlate with bacterial load and severity of infection, said Nivedita Srinivas, MD, a pediatric infectious disease specialist at Stanford (Calif.) University (*J Pediatr Intensive Care*. 2016 Dec;5[4]:162-71).

The presenters focused their talk on community acquired pneumonia (CAP) and invasive bacterial infections (IBI) in young infants, meaning essentially bacteremia and meningitis.

Different studies use different cutoffs, but a procalcitonin below, for instance, 0.5 ng/mL is “certainly more sensitive [for IBI] than any single biomarker we currently use,” including CRP, white blood cells, and absolute neutrophil count (ANC). “If it’s negative, you’re really confident it’s negative,” but “a positive test does not necessarily indicate the presence of IBI,” Dr. McCulloh said (*Pediatrics*. 2012 Nov;130[5]:815-22).

“Procalcitonin works really well as part of a validated step-wise rule” that includes, for instance, CRP and ANC; “I think that’s where its utility is. On its own, it is not a substitute for you examining the patient and doing your basic risk stratification, but it may enhance your decision making incrementally above what we currently have,” he said.

Meanwhile, in a study of 532 children a median age of 2.4 years with radiographically confirmed CAP, procalcitonin levels were a median of 6.1 ng/mL in children whose pneumonia was caused by *Streptococcus pneumoniae* or other typical bacteria, and no child infected with typical bacteria had a level under 0.1 ng/mL. Below that level, “you can be very sure you do not have typical bacteria pneumonia,” said Marie Wang, MD, also a pediatric infectious disease specialist at Stanford (*J Pediatric Infect Dis Soc*. 2018 Feb 19;7[1]:46-53).

As procalcitonin levels went up, the likelihood of having bacterial pneumonia increased; at 2 ng/mL, 26% of subjects were infected with typical bacteria, “but even in that group, 58% still had viral infection, so you are still detecting a lot of viral” disease, she said.

Procalcitonin-guided therapy – antibiotics until patients fall below a level of 0.25 ng/mL, for instance – has also been associated with decreased antibiotic exposure (*Respir Med*. 2011 Dec;105[12]:1939-45).

The speakers had no disclosures. The meeting was sponsored by the Society of Hospital Medicine, the American Academy of Pediatrics, and the Academic Pediatric Association.

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Many institutions exceed recommended CT scan radiation doses during lung cancer screening

BY ERIK GREB

MDedge News

A significant proportion of institutions that perform low-dose CT scan for lung cancer screening exceed the radiation dose levels that guidelines recommend, according to a study published in *JAMA Internal Medicine*.

Various institutional characteristics, such as allowing any radiologist to establish CT scan protocols, are associated with a greater likelihood of using higher radiation doses. “Dose optimization practices may benefit from being tailored to specific practice types, as well as different organizational structures, to have a higher likelihood of meeting dose guidelines,” wrote Joshua Demb, PhD, MPH, a cancer epidemiologist at the University of California, San Diego, and colleagues.

Lung cancer screening benefits patients when low-dose CT scan is used, but not when high-dose CT scan is used, because radiation from higher doses may cause as many cancers as are detected by screening. The Centers for Medicare & Medicaid Services require institutions to use low-dose techniques and participate in a dose registry to be reimbursed for lung cancer screening. The American College of Radiology recommends that lung cancer screening scans have a volume CT dose index (CTDIvol) of 3 mGy or lower and an effective dose (ED) of 1 millisieverts (mSv) or lower.

A prospective study of registry data

Dr. Demb and colleagues conducted a study to describe CT scan radiation doses for lung cancer screening in current practice and to identify the factors that explain variation in doses between institutions. They prospectively collected lung

cancer screening examination dose metrics from 2016 to 2017 at U.S. institutions participating in the University of California, San Francisco, International Dose Registry. Eligible institutions performed a minimum of 24 lung cancer screening scans during the study period. At baseline, the investigators surveyed institutions about their characteristics (for example, how they perform and oversee CT scans). Dr. Demb and colleagues estimated mixed-effects linear and logistic regression models using forward variable selection. They conducted their analysis between 2018 and 2019.

The researchers chose four outcome measures. The first was mean CTDIvol, reflecting the average radiation dose per slice. The second was mean ED, reflecting the total dose received and estimated future cancer risk. The third was the proportion of CT scans using radiation doses above ACR benchmarks. The fourth was the proportion of CT scans using radiation doses above the 75th percentile of registry doses (CTDIvol greater than 2.7 mGy and ED greater than 1.4 mSv).

Institutional characteristics and radiation dose

Dr. Demb and colleagues collected data from 72 institutions about 12,529 patients undergoing CT scans for lung cancer screening. Approximately 58% of patients were men, and the patients’ median age was 65 years. The mean CTDIvol, adjusted for patient size, was 2.4 mGy. The mean ED for lung cancer screening, adjusted for chest diameter, was 1.2 mSv.

A total of 15 institutions (21%) had a median adjusted CTDIvol value higher than the ACR guideline, and 47 (65%) had a median adjusted ED higher than the ACR guideline. Approximately 18% of CT scans had a CTDIvol higher

than guidelines, and 50% had an ED higher than ACR guidelines.

Institutions that permitted any radiologist to establish CT scan protocols had 44% higher mean CTDIvol and 27% higher mean ED, compared with institutions that restricted who could establish protocols. Institutions that permitted any radiologist to establish protocols also had higher odds of conducting examinations that exceeded ACR CTDIvol guidelines (odds ratio, 12.0) and of being in the 75th percentile of the registry CTDIvol (OR, 19.0) or ED (OR, 8.5) values.

In contrast, having lead radiologists establish CT scan protocols resulted in lower odds of using doses that exceeded ACR ED guidelines (OR, 0.01). Employing external, rather than internal, medical physicists was associated with increased odds of exceeding ACR CTDIvol guidelines (OR, 6.1). Having medical physicists establish protocols was associated with decreased odds of exceeding the 75th percentile of the registry CTDIvol (OR, 0.09) values. Institutions that updated protocols as needed, rather than annually, had 27% higher mean CTDIvol.

“Although we cannot establish causality in this observational study, our results suggest that considering these factors (for example, allowing only lead radiologists to establish protocols) could have a meaningful impact on dose, and could be important areas to develop interventions to optimize doses of CT protocols” the investigators wrote.

The Patient Centered Outcomes Research Institute and the National Institutes of Health supported this research. The authors reported no conflicts of interest.

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SOURCE: Demb J et al. *JAMA Intern Med*. 2019 Sep 23. doi: 10.1001/jamainternmed.2019.3893.

Molecular profiling a must in advanced NSCLC

BY NEIL OSTERWEIL

MDedge News

All patients with locally advanced or metastatic non–small cell lung cancer (NSCLC) should undergo molecular testing for targetable mutations and for tumor expression of the programmed death–ligand 1 (PD-L1) protein, authors of a review of systemic therapies for NSCLC recommend.

Their opinion is based on evidence showing that 5-year overall survival rate for patients whose tumors have high levels of PD-L1 expression now exceeds 25%, and that patients with ALK-positive tumors have 5-year overall survival rates over 40%. In contrast, 5-year survival rates for patients with metastatic NSCLC prior

to the 21st century were less than 5%, according to Kathryn C. Arbour, MD, and her colleagues of Memorial Sloan Kettering Cancer Center.

“Improved understanding of the biology and molecular subtypes of non–small cell lung cancer have led to more biomarker-directed therapies for patients with metastatic disease. These biomarker-directed therapies and newer empirical treatment regimens have improved overall survival for patients with metastatic non–small cell lung cancer,” they wrote in *JAMA*.

The authors reviewed published studies of clinical trials of medical therapies for NSCLC, including articles on randomized trials, non-randomized trials leading to practice changes or regulatory approval of

new therapies for patients with locally advanced or metastatic NSCLC, and clinical practice guidelines.

Their review showed that approximately 30% of patients with NSCLC have molecular alterations predictive of response to treatment, such as mutations in EGFR, the gene encoding for epidermal growth factor receptor; rearrangements in the ALK (anaplastic lymphoma kinase) and ROS1 genes; and mutations in BRAF V600E.

Patients with somatic activating mutations in EGFR, which occur in approximately 20% of those with advanced NSCLC, have better progression-free survival when treated with an EGFR-target tyrosine kinase inhibitor such as gefitinib, compared with cytotoxic chemotherapy.

The review was supported in part by a grant from the National Cancer Institute to Memorial Sloan Kettering. Dr. Arbour reported serving as a consultant to AstraZeneca and nonfinancial research support from Novartis and Takeda. Dr. Riely reported grants and nonfinancial support from Pfizer, Roche/Genentech/Chugai, Novartis, Merck, and Takeda; a patent pending for an alternative dosing of erlotinib for which he has no right to royalties; and payments from the National Comprehensive Cancer Network to participate in a committee overseeing solicitation and selection of grants to be awarded by AstraZeneca.

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SOURCE: Arbour KC et al. *JAMA*. 2019;322(8):764-74.

Prior antibiotic use lowers checkpoint inhibitor response and survival

BY BIANCA NOGRADY

MDedge News

Prior antibiotic use may be associated with a reduced treatment response to checkpoint inhibitors, and worse outcomes, in patients with cancer, according to investigators.

In a prospective cohort study, researchers followed 196 patients with cancer who were treated with immune checkpoint inhibitors in routine clinical practice.

A total of 22 patients had been treated with a 7-day or less course of broad-spectrum beta-lactam-based antibiotics in the 30 days prior to starting immune checkpoint inhibitor therapy, and 68 patients were concurrently taking broad-spectrum beta-lactam-based antibiotics with their checkpoint inhibitor therapy.

The analysis revealed that prior antibiotic therapy was associated with nearly a 100% greater likelihood of poor response to checkpoint inhibitor therapy (P less than .001) and significantly worse overall survival (2 vs. 26 months). Patients who had been on prior antibiotic therapy were also more likely to stop checkpoint inhibitor therapy because their disease had progressed, and were more likely to die of progressive disease while on checkpoint inhibitors.

However, concurrent antibiotic use did not appear to affect either treatment response to checkpoint inhibitors or overall survival.

The most common indication for both prior and concurrent antibiotic use was respiratory tract infections. Researchers examined whether cancer type might play a role in contributing to the association; for example, chronic airway disease in lung cancer might mean higher likelihood of antibiotic use but also lower treatment response and survival.

They found that the association between prior antibiotic therapy and overall survival was consis-

tent across the 119 patients with non-small cell lung cancer, the 38 patients with melanoma, and the 39 patients with other tumor types.

The association was also independent of the class of antibiotic used, the patient's performance status, and their corticosteroid use.

"Broad-spectrum ATB [antibiotic] use can cause prolonged disruption of the gut ecosystem and impair the effectiveness of the cytotoxic T-cell response against cancer, strengthening the biologic plausibility underlying the adverse effect of ATB therapy on immunotherapy outcomes," wrote David J. Pinato, MD, from Imperial College London, and coauthors in *JAMA Oncology*.

Addressing the question of whether comorbidities might be the mediating factor, the authors pointed out that the use of antibiotics during checkpoint inhibitor therapy – which was a potential indicator of patients' status worsening during treatment – was not associated with reduced response to treatment or lower overall survival.

"Although provision of cATB [concurrent antibiotic] therapy appears to be safe in the context of immunotherapy, clinicians should carefully weigh the pros and cons of prescribing broad-spectrum ATBs prior to ICI [immune checkpoint inhibitor] treatment," they wrote.

The study was supported by the Imperial College National Institute for Health Research Biomedical Research Centre, the Imperial College Tissue Bank, the Imperial Cancer Research U.K. Centre, the National Institute for Health Research, and the Wellcome Trust Strategic Fund. Two authors reported receiving grant funding and personal fees from the pharmaceutical sector unrelated to the study.

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SOURCE: Pinato DJ et al. *JAMA Oncol.* 2019 Sep 12. doi: 10.1001/jamaoncol.2019.2785.

NOTE CORRECTION: In the Critical Care Commentary "Changing clinical practice to maximize success of ICU airway management" in the August issue of *CHEST Physician*, please note a correction to the following sentence on page 27: The American College of Chest Physicians (CHEST) Difficult Airway Course faculty also initially recommended to not use NMB because of the high risk of failure to ventilate/oxygenate.

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Most practices not screening for five social needs

BY ALICIA GALLEGOS

MDedge News

A minority of physician practices and hospitals are screening patients for five key social needs that are associated with health outcomes, a study found.

Lead author Taressa K. Frazee, PhD, of the Dartmouth Institute for Health Policy and Clinical Practice in Lebanon, N.H., and colleagues conducted a cross-sectional survey analysis of responses by physician practices and hospitals that participated in the 2017-2018 National Survey of Healthcare Organizations and Systems. The investigators evaluated how many practices and hospitals reported screening of patients for five social needs: food insecurity, housing instability, utility needs, transportation needs, and experience with interpersonal violence. The final analysis included 2,190 physician practices and 739 hospitals.

Of physician practices, 56% reported screening for interpersonal violence, 35% screened for transportation needs, 30% for food insecurity, 28% for housing instability, and 23% for utility needs, according to the study published in *JAMA Network Open*.

Among hospitals, 75% reported screening for interpersonal violence, 74% for transportation needs, 60% for housing instability, 40% for food insecurity, and 36% for utility needs. Only 16% of physician practices and



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24% of hospitals screened for all five social needs, the study found, while 33% of physician practices and 8% of hospitals reported screening for no social needs. The majority of the overall screening activity was driven by interpersonal violence screenings.

Physician practices that served more disadvantaged patients, including federally qualified health centers and those with more Medicaid revenue were more likely to screen for all five social needs. Practices in Medicaid accountable care organization contracts and those in Medicaid expansion states also had higher screening rates. Regionally,

practices in the West had the highest screening rates, while practices in the Midwest had the lowest rates.

Among hospitals, the investigators found few significant screening differences based on hospital characteristics. Ownership, critical access status, delivery reform participation, rural status, region, and Medicaid expansion had no significant effects on screening rates, although academic medical centers were more likely to screen patients for all needs compared with nonacademic medical centers.

The study authors wrote that doctors and hospitals may need more resources and additional processes

to screen for and/or to address the social needs of patients. They noted that practices and hospitals that did not screen for social needs were more likely to report a lack of financial resources, time, and incentives as major barriers.

To implement better screening protocols and address patients' needs, the investigators wrote that doctors and hospitals will need financial support. For example, the Centers for Medicare & Medicaid Services should consider expanding care management billing to include managing care for patients who are both at risk or have clinically complex conditions in addition to social needs.

Dr. Frazee and three coauthors reported receiving grants from the Agency for Healthcare Research and Quality during the conduct of the study. Dr. Frazee also reported receiving grants from the Robert Wood Johnson Foundation during the conduct of the study and receiving grants as an investigator from the 6 Foundation Collaborative, Commonwealth Fund, and Centers for Disease Control and Prevention. One coauthor reported receiving grants from the National Institute on Aging/National Institutes of Health during the conduct of the study.

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SOURCE: Frazee TK et al. *JAMA Network Open*. 2019 Sep 18. doi: 10.1001/jamanetworkopen.2019.11514.

VIEW ON THE NEWS

Needed: Strategies for overcoming screening barriers

While momentum for social risk screening is growing nationally, the recent study by Frazee et al. illustrates that screening across multiple domains is not yet common in clinical settings, wrote Rachel Gold, PhD, of Kaiser Permanente Center for Health Research Northwest in Portland, Ore.

In an editorial accompanying the study, Dr. Gold and coauthor Laura Gottlieb, MD, an associate professor of family and community medicine at the University of California, San Francisco, wrote that a critical finding of the study is that reimbursement is associated with uptake of social risk screening (*JAMA Network Open*. 2019 Sep 18. doi: 10.1001/jamanetworkopen.2019.11513). Specifically, the analysis found that screening for social risks is more common in care settings that receive some form of payment to support

such efforts, directly or indirectly.

"This finding aligns with other research showing that altering incentive structures may enhance the adoption of social risk screening in health care settings," Dr. Gold and Dr. Gottlieb wrote. "But these findings are just a beginning. Disseminating and sustaining social risk screening will require a deep understanding of how best to structure financial and other incentives to optimally support social risk screening; high-quality research is needed to help design reimbursement models that reliably influence adoption."

Further research is needed not only to explain challenges to the implementation of social risk screening, but also to reveal the best evidence-based methods for overcoming them, the authors wrote. Such methods will likely require a range of support strategies targeted to the

needs of various health care settings.

"Documenting social risk data in health care settings requires identifying ways to implement such screening effectively and sustainably," Dr. Gold and Dr. Gottlieb wrote. "These findings underscore how much we still have to learn about the types of support needed to implement and sustain these practices."

Dr. Gold reported receiving grants from the National Institutes of Health during the conduct of the study. Dr. Gottlieb reported receiving grants from the Robert Wood Johnson Foundation, the Commonwealth Fund, Kaiser Permanente, Episcopal Health Foundation, the Agency for Healthcare Research and Quality, St. David's Foundation, the Pritzker Family Fund, and the Harvard Research Network on Toxic Stress outside the submitted work.

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FROM THE PRESIDENT

Wisdom of our crowd

BY CLAYTON T. COWL, MD, MS, FCCP

About a year ago, I had the opportunity to don the honorary regalia of the American College of Chest Physicians as its 81st President. On that memorable day on the dais in San Antonio, I used the example of James Surowiecki's book, "The Wisdom of Crowds: Why the Many Are Smarter than the Few and How Collective Wisdom Shapes Business, Economics, Societies, and Nations" to explain how we would use the collective wisdom of our members, our committee and NetWork members, and our talented association staff to build and shape CHEST over the coming year. For those of you not familiar with this concept, Surowiecki, a business columnist for New Yorker, outlines the concept that large groups of people are actually smarter than an elite few at solving the problems of an organization, fostering innovation, collectively coming to wise decisions, or even predicting the future. In channeling the lessons from the book, it has become obvious that listening to our members and partners, rather than trying to make all decisions from the top down, has been an effective method for coming to wise decisions about the strategy and operation of CHEST. Now that it's already time to hand the responsibility of the organization as President over to my friend and colleague Dr. Stephanie Levine, I've reflected on actually how effectively we have listened and how smart the collective crowd has been in moving the success of CHEST forward.

We heard from members that it was difficult to know how to get involved and what happens at the highest leadership levels of the organization. This prompted the development of podcasts dubbed "The Inside Scoop," recorded live approximately every 2 months and features various leaders of the organization with an informal way for members to better understand how to become involved in CHEST activities and to feel the pulse of activity of the association between the time the annual meeting ends and the next one begins.

The crowd informed us that communication at the Board of Regents level could be better. To address this, regular communications were sent out to the Board of Regents to update them on activities and discussion of issues between scheduled board meetings, as well as providing board members the opportunity to have access to the minutes of phone calls of the "5Ps," calls that included the Immediate Past President, President-Elect, President-Designate, and current President of the association, as well as the CHEST Foundation President.

We were told by members through focus groups and surveys, then again told by experts we invited to the June board meetings from education, business, design, and venture capital sectors (and who were naïve to CHEST as an association) that we needed to double down on virtual educational offerings to learners across the health-care delivery team and to revamp the information technology infrastructure. To that end, a digital



Dr. Clayton T. Cowl

strategy work group was convened with expertise in information technology, social media, and marketing to inventory all digital assets of the College and make recommendations for not just improvement, but for a complete transformation of digital technology created and promulgated

"The collective wisdom of our members, talented clinicians and researchers, and colleagues in industry has provided incredibly valuable input to the CHEST leadership team. You have spoken, and we have been listening. Thanks to each of you who have reached out to me during this year as President."

by CHEST. The board then approved a budget of nearly \$1 million to upgrade and rebuild the user experience within CHEST's digital environment, including its learning management system. We also opened a multimedia studio at CHEST headquarters, increased the numbers of serious educational gaming opportunities at the annual meeting, and are developing a line of serious game platforms that will allow for "edutainment" opportunities for our members and other learners around the world using various digital platforms.

Colleagues from around the world reminded us that 20% of CHEST membership was international and that our strategic plan included an international strategy. Thanks to the support of our colleagues around the world, we were able to enjoy a tremendously successful CHEST Congress in Bangkok, Thailand, in April, and a smaller regional meeting in June in Athens, Greece. Efforts of the Governance Committee have reshaped the structure of international representation, mak-

ing it more relevant and allowing its members to have a stronger voice to the Board of Regents. Plans are underway for the next CHEST Congress in June 2020 in Bologna, Italy, to be held in collaboration with the Italian Chapter of CHEST in that country.

In an era when the majority of association annual meetings across multiple specialties is driving toward parity with similar looks, marketing, formats, and expectations, we listened to the needs and desires of attendees of last year's meeting and have improved CHEST 2019 in New Orleans even more. With the most simulation courses ever delivered at an annual meeting, more serious game opportunities, CHEST Challenge finals, a new innovation competition called "FISH Bowl," and even a medical escape room, CHEST volunteer leaders and organization staff have worked hard to provide a world class meeting that has a different look and feel from all the others. Plus, the crowd also told us that having CME and MOC credit available for the entire meeting was another variable that was desired, and has now been achieved.

The wisdom of the proverbial crowd of membership has spoken in terms of the need for philanthropic efforts in our specialty. The CHEST Foundation has responded by awarding tens of thousands of dollars to our members to recognize cutting-edge research, community service efforts, and, in addition, has allowed dozens of providers early on in training or in their career to attend the annual meeting with the help of travel grants.

CHEST guidelines continue to be updated and new ones created based on input from expert panel teams. The CHEST journal submission process, review turnaround times, and quality of manuscripts have improved each year thanks to useful feedback from authors and readers. Publications such as CHEST Physician are modified each year based upon feedback from our readers. Critiques from the board review courses have been the driving force keeping live learning formats and the electronic SEEK board preparation questions current and accurate when the science is constantly changing.

Truly, the collective wisdom of our members, talented clinicians and researchers, and colleagues in industry has provided incredibly valuable input to the CHEST leadership team. You have spoken, and we have been listening. Thanks to each of you who have reached out to me during this year as President. Traveling to four continents this past year to better understand the needs of members who are clinicians, educators, researchers, and caregivers positioned in each geographic region has been enlightening, educational, and transformative for me and my family. Your meaningful feedback, keen insights, and passion for outstanding patient care, impactful educational experiences, and life-changing research have helped to push CHEST to a higher level of excellence and to offer unparalleled experiences for our members to ultimately provide the very best care to patients.

E-cigarette-associated respiratory diseases: Ask your patients about vaping substances

BY SANDRA G. ADAMS, MD, MS, FCCP

E-cigarettes arrived in the U.S. market between 2005 and 2007. Vaping via e-cigarettes involves inhaling substances such as nicotine, flavorings, chemicals, and, sometimes, marijuana and/or other substances deep into the lungs. While the use of these devices is prevalent, the long-term effects are not known. We, as clinicians, need to specifically ask our patients about their use of substances via e-cigarettes because of alarming cases of severe, life-threatening respiratory illnesses recently being reported throughout the United States in young, otherwise healthy, individuals.



Dr. Adams

As of September 17, 2019, over 539 cases have been reported to the Centers for Disease Control and Prevention (CDC), where young, healthy people from 38 states and one US territory were hospitalized with severe respiratory disease. There have been at least seven confirmed deaths* and approximately one-third of those who survived required aggressive support with intubation and mechanical ventilation. The number of reported cases is rapidly rising (from 215 possible cases on August 27, 2019). The common theme in these cases is that every patient reported using an e-cigarette product within 90 days of the onset of symptoms, and most within the prior 2 weeks. By definition, other etiologies of respiratory failure, such as infections, collagen vascular, immunologic diseases, and malignancies were excluded.

Between 90% and 98% of patients presented to the hospital with respiratory symptoms, such as shortness of breath, cough, hemoptysis, and/or chest pain. The most common reported e-cigarette product exposure among these case patients is tetrahydrocannabinol, THC (in approximately 80% to 85%); however, some used only nicotine-based products (15% to 20%). In addition, approximately 45% to 50% reported using THC and nicotine-based products. One concerning fact that requires special attention is that some affected patients initially presented with nonrespiratory complaints, such as GI symptoms of nausea, vomiting, and/or diarrhea; constitutional symptoms such as fever (up to 104°F), fatigue, and/or weight loss; and neurologic symptoms such as headaches and even seizures. Many of these symptoms preceded the respiratory symptoms by up to 2 weeks. Therefore, a few of these patients initially presented without significant respiratory symptoms and with normal chest radiographs – but progressed over days to weeks to acute hypoxemic respiratory failure.

Up to 75% of the affected patients who ultimately required hospitalization for e-cigarette-associated respiratory disease initially presented to a primary care clinic or ED and were sent home

due to nonspecific signs and symptoms, which mimic common viral illnesses. Therefore, it is critical for all health-care professionals to have a high clinical suspicion for e-cigarette-associated respiratory disease, particularly while more data are being gathered. When suspected, the CDC recommends asking patients about specific substances inhaled, the manufacturer, where the products/cartridges were obtained, type of device(s) used, and method used (ie, aerosolization, dabbing, dripping, etc).

The most common types of imaging and pathologic patterns attributed to e-cigarette use reported to date include lipoid pneumonia, diffuse alveolar damage, acute respiratory distress syndrome (ARDS), diffuse alveolar hemorrhage (DAH), acute eosinophilic pneumonia, hypersensitivity pneumonitis, and organizing pneumonia. The most common patterns on imaging include basilar-predominant consolidation and ground-glass opacities with areas of subpleural sparing. In addition, approximately 10% to 15% of the reported cases had a spontaneous pneumothorax, pneumomediastinum, and/or associated pleural effusions. Bronchoscopy specimens, such as bronchoalveolar lavage (BAL) and transbronchial biopsies (TBBx), were often but not always ob-

tained. In patients who underwent bronchoscopy, many were found to have lipid-laden alveolar macrophages. These findings were discovered by staining fresh (ie, those not placed in fixative) specimens from BAL and/or TBBx for lipids with oil red O or another stain to specifically detect fat within the samples. Other etiologies of these radiographic/pathologic patterns and conditions should be excluded, as listed above.

The clinical course varies widely among these reported cases of vaping and e-cigarette-associated respiratory diseases. A minority of the reported patients spontaneously improved, and others required significant supportive care – from supplemental oxygen to complete support with ECMO. Some were treated with systemic corticosteroids with a wide range of responses and with various dosages: from prednisone of 0.5 to 1 mg/kg up to pulse-dose steroids with 1 g methylprednisolone for 3 days with a slow taper.

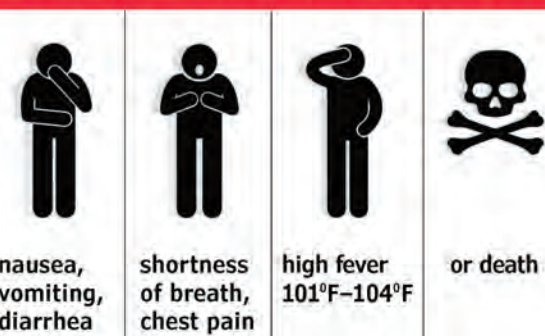
The information and data reported about these e-cigarette-associated respiratory diseases are clearly evolving quickly and vary from center to center and state to state. All suspected cases should be reported to your state health department. Similar to other inhalational injuries, it is critical to monitor these patients following recovery from the acute illness to help determine the long-term pulmonary effects and clinical courses of these individuals. Offering assistance and treatment for addiction is also important in these patients to help reduce their chances of recurrent respiratory problems from ongoing exposure to these substances in e-cigarettes. The bottom line is that cases of e-cigarette-associated respiratory diseases are increasing rapidly throughout the United States. Therefore, we should all be vigilant about asking our patients about their use of these substances and providing clear and strong messages for each of our patients to avoid vaping any substances through e-cigarettes.

Dr. Adams is Professor of Medicine, Pulmonary/Critical Care Division, Distinguished Teaching Professor, UT Health San Antonio; Staff Physician, South Texas Veterans Health Care System, San Antonio, Texas



Do you vape...
nicotine, THC, cocaine, others?

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***As the vaping statistics are changing daily, the reported numbers in this report are as of September 17, 2019.**

ENVIRONMENTAL SCAN

Drivers of change in education, content delivery, and career advancement

BY THERESE BORDEN

MDedge News

Keeping up to date and maintaining currency on developments in medicine are a routine part of medical practice, but the means by which this is accomplished are changing rapidly. Training, maintenance of certification, continuing education, mentoring, and career development will all be transformed in the coming years because of new technology and changing needs of physicians. Traditional learning channels such as print media and in-person courses will give way to options that emphasize ease of access, collaboration with fellow learners, and digitally optimized content.

Education and content delivery

The primary distribution channels for keeping medical professionals current in their specialty will continue to shift away from print publications and expand to digital outlets including podcasts, video, and online access to content.¹ Individuals seeking to keep up professionally will increasingly turn to resources that can be found quickly and easily, for example, through voice search. Content that has been optimized to appear quickly and with a clear layout adapted to a wide variety of devices will most likely be consumed at a higher rate than resources from well-established organizations that have not transformed their continuing education content. There is already a growing demand for video and audiocasts accessible via mobile device.²

John D. Buckley, MD, FCCP, professor of medicine and vice chair for education at Indiana University, Indianapolis, sees the transformation of content delivery as a net plus for physicians, with a couple of caveats. He noted, “Whether it is conducting an in-depth literature search, reading/streaming a review lecture, or simply confirming a medical fact, quick access can enhance patient care and advance learning in a manner that meets an individual’s learning style. One potential downside is the risk of unreliable information, so accessing trustworthy sources is essential. Another potential downside is that, while accessing the answer to a very specific question can be done very easily, this might compromise additional learning of related material that used to occur when you had to read an entire book chapter to answer your question. Not only did you answer your question, you learned a lot of other relevant information along the way.”

Online learning is now a vast industry and has been harnessed by millions to further professional learning opportuni-

ties. Massive Open Online Courses (MOOCs) are free online courses available for anyone to enroll.³ MOOCs have been established at Harvard, MIT, Microsoft, and other top universities and institutions in subjects like computer science, data science, business, and more. MOOCs are being replicated in conventional universities and are projected to be a model for adult learning in the coming decade.⁴



Dr. Buckley

Another trend is the growing interest in microlearning, defined as short educational activities that deal with relatively small learning units utilized at the point where the learner will actually need the information.⁵ Dr. Buckley sees potential in microlearning for continuing medical education. “It is unlikely that microlearning would be eligible for CME currently unless there were a mechanism for aggregating multiple events into a substantive unit of credit. But the ACCME [Accreditation Council for Continuing Medical Education] has been

very adaptive to various forms of learning, so aggregate microlearning for CME credit may be possible in the future.” He added that the benefits of rapid and reliable access to specific information from a trusted source are significant, and the opportunities for microlearning for chest physicians are almost limitless. “Whether searching for the most updated review of a medical topic, or checking to see if your ICU patient’s sedating medication can cause serotonin syndrome, microlearning is already playing a large role in physician education, just less formal than what’s been used historically,” he said.

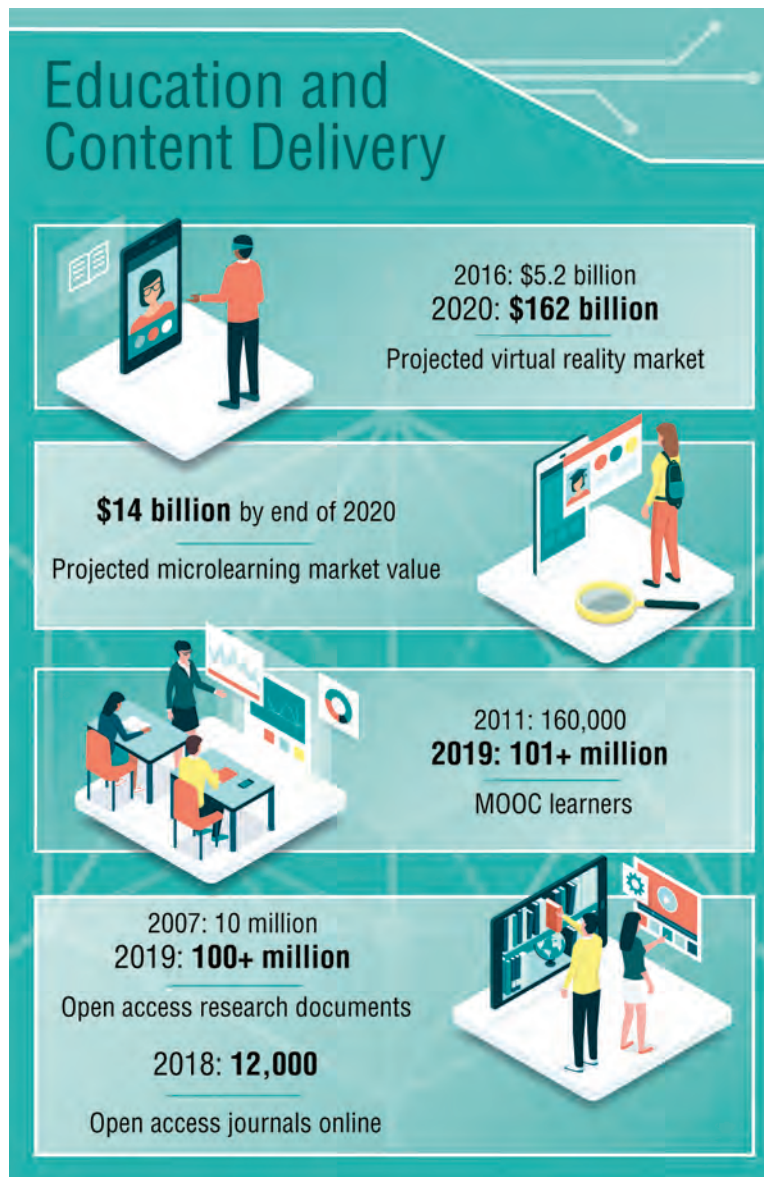
Institutions for which professional development learning modules are an important revenue stream will increasingly be challenged to compete with open-access courses of varying quality.

A key trend identified in 2018 is accelerating higher-education technology adoption and a growing focus on measured outcomes and learning.⁵ Individuals are interested in personalized learning plans and adaptive learning systems that can provide real-time assessments and immediate feedback. It is expected that learning modules and curricula will be most successful if

they are easily accessed, attractively presented, and can incorporate immediate feedback on learning progress. Driving technology adoption in higher education in the next 3-5 years will be the proliferation of open educational resources and the rise of new forms of interdisciplinary studies. As the environment for providing and accessing content shifts from pay-to-access to open-access, organizations will need to identify a new value proposition if they wish to grow or maintain related revenue streams.⁶

The implications of these changes in demand are profound for creators of continuing education content for medical professionals. Major investment will be needed in new, possibly costly platforms that deliver high-quality content with accessibility and interactive elements to meet the demands of professionals, the younger generation in particular.⁷

The market will continue to develop new technology to serve continuing education needs and preferences of users, thus fueling competition among stakeholders. With the proliferation of free and low-cost online and virtual programs, continuing education providers may experience a negative impact on an important revenue stream if they don’t identify a competitive advantage that meets the needs of tomorrow’s workforce. However, educational programs and courses that use artificial intelligence, virtual reality, and augmented reality to enhance the learning experience are likely to experience higher levels of use in the coming years.⁸



Workforce diversity and mentoring

A global economy requires organizations to seek a diverse workforce. Diversity can also lead to higher levels of profitability and employee satisfaction. As such, it will be essential for organizations to increase opportunities for individuals from diverse backgrounds to join the workforce. Creating a diverse workforce will mean removing barriers of time and location to skill building through online learning opportunities and facilitation of interdisciplinary career paths.

A critical piece of the emerging model of career development will be mentoring. Many professionals in today's workforce view mentoring as an opportunity to gain immediate skills and knowledge quickly and effectively. Mentoring has evolved from pairing young professionals with seasoned veterans to creating relationships that match individuals with others who have the skills and knowledge they desire to learn about – regardless of age and experience. Institutions striving to develop a diverse workforce will need many individuals to serve as both mentors and mentees. When searching for solutions to work-related challenges, individuals will increasingly turn to knowledge management and collaboration systems (virtual mentoring) that provide them with the opportunity to match their needs in an efficient and effective manner.

Dr. Buckley values peer-to-peer mentoring as a means of accessing

and sharing niche expertise among colleagues, but he acknowledges the difficulties in incorporating it into everyday practice. “The biggest obstacles are probably time and access. More and more learners and mentors are recognizing the tremendous value of effective mentorship, so convincing people is less of an issue than finding time,” he said.

Mentorship will continue to play a central role in the advancement of one's career, yet women and minorities find it increasingly difficult to match with a mentor within the workplace. These candidates are likely to seek external opportunities. Individuals will evaluate the experience, opportunities for career advancement, and the level of diversity and inclusion when seeking and accepting a new job.

Dr. Buckley sees both progress and remaining challenges in reducing barriers to underrepresented groups in medical institutions. “There continues to be a need for ongoing training to help individuals and institutions recognize and eliminate their barriers and biases, both conscious and subconscious, that interfere with achieving diversity and inclusion. Another important limitation is the pipeline of underrepresented groups that are pursuing careers in medicine. We need to do more empowerment, encouragement, and recruitment of underrepresented groups at a very early stage in their education if we ever expect to achieve our goals.”

Future challenges

The transformations described above will require a large investment by physicians aiming to maintain professional currency, by creators of continuing education content, and by employers seeking a diversified workforce. All these stakeholders have an interest in the future direction of continuing education and professional training. The development of new platforms for delivery of content that is easily accessible, formatted for a wide variety of devices, and built with real-time feedback functions will require a significant commitment of resources.

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Note: Background research performed by Avenue M Group.

CHEST Inspiration is a collection of programmatic initiatives developed by the American College of Chest Physicians leadership and aimed at stimulating and encouraging innovation within the association. One of the components of CHEST Inspiration is the Environmental Scan, a series of articles focusing on the internal and external environmental factors that bear on success currently and in the future. See “Envisioning the Future: The CHEST Environmental Scan,” *CHEST Physician*, June 2019, p. 44, for an introduction to the series.

This month in the journal CHEST®

Editor's picks

BY PETER J. MAZZONE, MD, MPH, FCCP

Editor in Chief

ORIGINAL RESEARCH

The Saint Georges Respiratory Questionnaire definition of chronic bronchitis may be a better predictor of COPD exacerbations compared to the classic definition.
By Dr. V. Kim, et al.

Confocal laser endomicroscopy (CLE) as a guidance tool for pleural biopsies in malignant pleural mesothelioma.

By Dr. L. Wijmans, et al.



Association of Angiotensin Modulators With the Course of Idiopathic Pulmonary Fibrosis.

By Dr. M. Kreuter, et al.

Age-Stratified National Trends in Pulmonary Embolism Admissions.

By Dr. E. D. Pauley, et al.

COMMENTARY

Solving the Opioid Crisis: Respiratory Depression by Opioids as Critical Endpoint.

By Dr. G. Montandon and Dr. A. S. Slutsky.



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Coding changes coming soon

BY MICHAEL NELSON, MD, FCCP

CHEST Physician Editorial Board

There may be some positive changes coming to evaluation and management (E/M) services effective January 1, 2021. In the proposed calendar year 2020 Physician Fee Schedule (CY 2020



Dr. Nelson

These changes are predicted to result in a simplification of physician documentation and a redistribution of payments favoring providers who deliver primary care or care to more complex patients.

PFS), the Centers for Medicare & Medicaid Services (CMS) suggested a number of coding, payment, and documentation changes for office/outpatient E/M visits, Current Procedural Terminology (CPT[®]) codes 99201-99215. A summary of these changes include:

- Separate payment for the five levels of office/outpatient E/M visit CPT codes, as revised by the CPT Editorial Panel effective January 1, 2021. This would include deletion of CPT code 99201 (Level 1 new patient office/outpatient E/M visit) and adoption of the revised CPT code descriptors for CPT codes 99202-99215;
- Elimination of the use of history and/or physical exam to select among code levels;
- Choice of time or medical decision making to decide the level of office/outpatient E/M visit (using the

revised CPT interpretive guidelines for medical decision making);

- Payment for prolonged office/outpatient E/M visits using the revised CPT code for such services, including separate payment for new CPT code 99XXX and deletion of Healthcare Common Procedure Coding System (HCPCS) code GPRO1 (extended office/outpatient E/M

visit) that was previously finalized for 2021;

- Revise the descriptor for HCPCS code GPC1X and delete HCPCS code GCG0X; and

• Increase in value for HCPCS

code GPC1X and allowing it to be reported with all office/outpatient E/M visit levels.

These changes were recommended by CMS to improve payment accuracy, reduce the administrative burden, and better reflect the current practice of medicine. These changes are predicted to result in a simplification of physician documentation and a redistribution of payments favoring providers who deliver primary care or care to more complex patients.

In CY 2019 PFS, CMS proposed to pay a single (blended) rate for office/outpatient visits 2-4, but due to comments from stakeholders, including specialty societies, CMS proposed to accept alternate recommendations by AMA/CPT. These recommendations include using medical decision making or time to

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December 13 - 14

Advanced Critical Care Echocardiography Board Review Exam Course

TABLE 1: Comparison of Current Office/Outpatient E/M Services Code Set vs CY2021 Prolonged Services Code

CPT code	Current time	Current RVU	Proposed time	Proposed RVU
99201	17	0.48	NA	NA
99202	22	0.93	22	0.93
99203	29	1.42	40	1.6
99204	45	2.43	60	2.6
99205	67	3.17	85	3.5
99211	7	0.18	7	0.18
99212	16	0.48	18	0.70
99213	23	0.97	30	1.30
99214	40	1.50	49	1.92
99215	55	2.11	70	2.8
99XXX	NA	NA	15	0.61

CRITICAL CARE COMMENTARY

Should PEEP be titrated based on esophageal pressures?

BY ALICE GALLO DE MORAES, MD, AND RICHARD A. OECKLER, MD, PHD

Application of basic physiology principles at bedside has changed the approach to the treatment of patients with acute respiratory distress syndrome (ARDS) and refractory hypoxemia.

Current standard of care for patients with ARDS includes a low tidal volume ventilation strategy (6 mL/kg of ideal body weight), keeping plateau pressures below 30 cm H₂O (Brower RG, et al. *N Engl J Med.* 2000;342[18]:1301), driving pressures below 15 cm H₂O and adequate positive end-expiratory pressures (PEEP) to keep the alveoli open without overdistension (Villar J, et al. *Crit Care Med.* 2006;34[5]:1311). However, at this time, despite the awareness of the importance of this intervention, there is no consensus regarding the best method to determine ideal PEEP at the individual patient level.

A thorough understanding of the basic physiologic concepts regarding respiratory pressures is of paramount importance to be able to formulate an opinion. The transpulmonary pressure (or lung distending pressure) is the gradient caused by the difference between alveolar (PA) and pleural pressure (PPL). In order to prevent lung collapse at end-expiration, PA must remain higher than PPL such that the gradient remains outward, preventing end-expiratory collapse and

atelectotrauma. To accomplish that, it is necessary to know the end-expiratory PA and PPL. Esophageal balloon pressures (PES) represent central thoracic pressures, but, despite positional and regional variations, they are a good surrogate for average “effective” PPL (Baedorf KE, et al. *Med Klin Intensivmed Notfmed.* 2018;113[Suppl 1]:13).

Understanding that the value of the PES represents a practical PPL makes it easier to appreciate the potential usefulness of an esophageal balloon to titrate PEEP. The objective of PEEP titration is to prevent de-recruitment, maintain alveolar aeration, and improve the functional size of aerated alveoli. If the applied PEEP is lower than the PPL, the dependent lung regions will collapse. On the other hand, if PEEP is higher than the PPL, the lung would be overdistended, causing barotrauma and hemodynamic compromise.

The question is: Should we use esophageal balloons? Yes, we should.

A single center randomized control trial (EPVent) compared PEEP titration to achieve a positive PL vs standard of care lung protective ventilation

(Talmor D, et al. *N Engl J Med.* 2008;359:2095). The PEEP titration group used significantly higher levels of PEEP, with improved oxygenation and lung compliance. However, there was no significant difference in ventilator-free days or mortality between the groups.

Obese patients are also likely to benefit from PEEP titration guided by an esophageal balloon, as they often have higher levels of intrinsic PEEP. Therefore, the application of higher levels of PEEP

to compensate for the higher levels of intrinsic PEEP may help reduce work of breathing and prevent tidal recruitment-de-recruitment and atelectasis. Additionally, low to negative transpulmonary pressures measured using the actual values of PES in obese patients and obese animal models predicted lung collapse and tidal opening and closing (Fumagalli J, et al. *Crit Care Med.* 2017;45[8]:1374).

It is useful to remember that the compliance of the respiratory system (Crs) is the total of the sum of the compliance of the chest wall (Ccw) and the lung compliance (CL). In obese patients, Ccw has a much more significant contribution to the total Crs, and the clinician should be really

Continued on page 61



Dr. Gallo de Moraes



Dr. Oeckler

Continued from previous page

determine the level of a visit, rather than the schema that was based on history and physical exam and outlined in the 1995/1997 guidelines. This resulted in elimination of CPT code 99201 and changes to the descriptors of 99202-99215. These codes were resurveyed by the Relative Value Update Committee (RUC) resulting in new values and times. (See Table 1).

One can see that there has been an incremental increase in time and value for most codes. When selecting a code based upon time, there is a range that is defined for each code, and additional information about the codes, including the descriptors and ranges, can be found on the AMA website <https://www.ama-assn.org/cpt-evaluation-and-management>.

For CPT codes 99205 and 99215 (level 5 codes), an add-on code has also been proposed that would account for additional time spent above the new levels defined in the codes. The descriptor for CPT 99XXX (the final numbers have not yet been

TABLE 2: Total Proposed Practitioner Times for Office/Outpatient E/M Visits When Time Is Used to Select Visit Level

Total time	CPT code
Established Patient Office/Outpatient E/M Visit	
40-54 minutes	99215
55-69 minutes	99215 *1 and 99XXX *1
70-84 minutes	99215 *1 and 99XXX *2
85 or more minutes	99215 *1 and 99XXX *3 or more for each additional 15 minutes
New Patient Office/Outpatient E/M Visit	
60-74 minutes	99205
75-89 minutes	99205 *1 and 99XXX *1
90-104 minutes	99205 *1 and 99XXX *2
105 or more minutes	99205 *1 and 99XXX *3 or more for each additional 15 minutes

assigned) reads *Prolonged office or other outpatient evaluation and management service(s) (beyond the total time of the primary procedure which has been selected using total time), requiring total time with or without direct patient contact beyond the usual service, on the date of the primary service; each 15 minutes (List separately in addition to codes 99205, 99215 for office or other outpatient Evaluation and Management services).* 99XXX is

similar to CPT add-on code 99292 in that it may be used multiple times for a single encounter. This is illustrated in Table 2.

However, 99XXX is only used with level 5 codes. It will replace HCPCS code GPRO1, which had been finalized in the CY 2019 PFS. The proposed code will have a value of 0.61 RVU.

Finally, there is a proposal to revise the descriptor for HCPCS code

GPC1X and eliminate HCPCS code GCG0X. The new descriptor for GPC1X *Visit complexity inherent to evaluation and management associated with medical care services that serve as the continuing focal point for all needed health care services and/or with medical care services that are part of ongoing care related to a patient's single, serious, or complex chronic condition. (Add-on code, list separately in addition to office/outpatient evaluation and management visit, new or established)* is being updated to simplify the coding and, with the elimination of GCG0X, to remove the perception that the code is primary care or specialty specific. The value of GPC1X is also being increased to 0.33 RVU.

It must be made clear that these changes are proposals only, and CMS is still reviewing stakeholder and public comments. Any actual changes will not be codified until publication of the CY2020 PFS later this year. Additional information regarding the proposed rule can be found by accessing <https://federalregister.gov/d/2019-16041>.

The emerging role of quantitative CT scans in ILD

BY SAMANTHA D'ANNUNZIO, MD;
CHRISTINE NAYAR, MD; AND
NINA PATEL, MD, FCCP

The role of imaging for interstitial lung disease (ILD) is of paramount importance. With the growth of high resolution chest computed tomography (HRCT) imaging techniques, we are able to visualize nuances between individual ILDs more critically.

HRCT is an essential component of an initial ILD evaluation and also has become part of the armamentarium of tools used for routine management of these patients. The technology of HRCT scans has evolved over the years, most recently with the advent of quantitative HRCT (qCT). The technology employs texture-based classification, which identifies and quantifies different radiographic findings. The arrival of qCT scanning has been slowly emerging as a new player in the ILD world. What exactly is qCT, and what role can, and will, it serve for our ILD patients?

Quantitative CT scanning was introduced in the 1980s, but only within the last 15 years has its use for ILD taken form. Human interpretation of CT scanning is fraught with subjectivity, based on the interpreting radiologist's training, experience, and individual visual perception of images. This can result in significant variability in radiographic interpretations and, ultimately, affects a patient's diagnosis, disease monitoring, treatment, and prognosis. Semiquantitative visual scoring by radiologists is highly variable, especially in areas with limited availability of chest radiologists. qCT employs an automated histogram signature technique that utilizes density and texture-based analysis of the lung parenchyma.

Utilizing machine learning from pathologically

confirmed datasets, computer programs were trained with specialized thoracic radiologists to distinguish some commonly found radiographic abnormalities into four major groups: ground glass, reticular, honeycombing, and emphysema. In addition, these categories are quantified and spatially depicted on an analysis (Bartholmai, et al. *J Thorac Imaging*. 2013;28[5]:298).

The technology employs texture-based classification, which identifies and quantifies different radiographic findings.

Various computer programs have been built to streamline the process and expedite the interpretation of an individual's HRCT scan. The more commonly familiar program, CALIPER (Computer-Aided Lung Informatics for Pathology Evaluation and Ratings), has been used in multiple research studies of qCT in ILD and IPF. Each patient's CT scan is uploaded to the program, and a breakdown of the patient's lungs into each category is presented. Not only is each abnormality quantified and precisely defined, it is also color-coded by segments to help with visual interpretation by the physician.

The benefit of qCT lies not only in the automated, objective evaluation of interstitial lung disease, but also in its possible use in prognostication and mortality prediction. Neither use has been fully validated as of yet. However, growing evidence shows a promising role in both realms. Thus far, there have been some studies correlating PFT data with qCT findings.

A follow-up study of the Scleroderma Lung Study II examined qCT changes over 24 months and correlated those findings with PFTs and patient-reported outcomes. Patients in this study

were either treated with cyclophosphamide (CYC) for 1 year/placebo 1 year vs mycophenolate mofetil (MMF) for 2 years. A large portion of patients receiving CYC or MMF had a significant correlation between improved or stable qCT scores and their FVC and TLC. Neither CYC nor MMF was superior in qCT scores, aligning with the findings of the study, which showed noninferiority of MMF compared with CYC (Goldin, et al. *Ann Am Thorac Soc*. 2018 Nov;15[11]:1286). Interestingly, the improvement of ground glass is often viewed by physicians as positive, since this finding is typically thought of as active inflammation. However, if qCT determines that the fibrosis score actually increases over time, despite an improvement in ground glass, this may more accurately reflect the development of subtle fibrosis that is not easily appreciated by the human eye (Goldin, et al. *Ann Am Thorac Soc*. 2018 Nov;15[11]:1286). In this context, it is feasible that parenchymal changes occur prior to deterioration on PFTs. Diffusing capacity for carbon monoxide (DLCO) correlates largely with the extent of lung involvement on qCT, but DLCO is not a specific biomarker in predicting severity of ILD (ie, because pHTN or anemia can confound DLCO). Forced vital capacity (FVC) in certain diseases may also confound CT correlation (ie, muscle weakness or extrathoracic restriction from skin disease in systemic sclerosis). The usefulness of PFT data as a clinical endpoint in research studies may be replaced by qCTs more consistent and precise detection of disease modification.

IPF has been an interesting area of exploration for the role of qCT in disease monitoring and possible prognostication. It is known that the presence of honeycombing on HRCT is asso-

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interested in the CL. At the bedside, esophageal manometry can be very useful to distinguish the contribution of CL and Ccw to the total Crs.

No, we shouldn't.

Another randomized controlled trial (EPVent-2), by the same group, compared PEEP titration guided by esophageal pressure with empirical PEEP titration, in patients with moderate to severe ARDS (Beitler JR, et al. *JAMA*. 2019;321[9]:846). The primary outcomes of interest, death, and mechanical ventilator-free days through day 28 were not different between the groups.

Additionally, placement of an esophageal balloon is challenging and operator-dependent. The balloon portion of the esophageal catheter should be positioned in the lower third of the esophagus, behind the heart. Catheter placement is

typically performed by inserting it into the stomach to a depth of about 60 cm, and gently pressing on the abdomen and observing a sudden increase in pressure on the ventilator screen. It is then withdrawn to about 40 cm, while looking for cardiac oscillations and pressure change (Talmor D, et al. *N Engl J Med*. 2008;359:2095). One can see how easily it would be to insert the esophageal balloon incorrectly. A misplaced balloon won't provide accurate PES and can potentially cause harm.

Final answer: It depends on each individual patient.

Arguments for and against using an esophageal balloon to titrate PEEP in patients with ARDS and refractory hypoxemia are ongoing. Even the two most cited and applied trials on the matter (EPVent and EPVent-2)

reported contradictory results. However, when analyzed in depth, both showed better oxygenation with the use of esophageal balloon. EPVent had improvement in oxygenation as its primary endpoint, and it was significant in the esophageal balloon group. EPVent-2 had oxygenation goals, in the form of need for rescue therapies for refractory hypoxemia, as secondary endpoints. Nonetheless, the patients in the esophageal balloon group in EPVent-2 required prone positioning less frequently, had lower use of pulmonary vasodilators, and a lower rate of ECMO consultations. Even though those trials did not show a mortality benefit, both showed an oxygenation benefit.

The ideal single tool that would indicate the "perfect" PEEP for each patient remains to be described. Until then, PEEP titration guided by a combination of ARDSnet PEEP

tables, while maintaining a plateau pressure below 30 cm H₂O and considering a driving pressure below 15 cm H₂O should be a clinician's goal. In patients in the extremes of height and body weight, and/or with conditions that would increase intra-abdominal pressure, such as ascites, a well-placed esophageal balloon while patient is supine might be beneficial.

The truth of the matter is, PEEP should be titrated by a trained intensivist in conjunction with the multidisciplinary ICU team, at patients' bedside taking into consideration each individual's unique physiologic and pathophysiologic characteristics at that moment.

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CHEST NETWORKS

Robotic-assisted bronchoscopy. PARDS. Vaping alert. PR and COPD.

Interventional Chest/ Diagnostic Procedures Emergence of robotic- assisted bronchoscopy for the diagnosis of peripheral lung lesions

The diagnostic chest medicine community saw exciting advances in technology for diagnosis of peripheral lung lesions (PLL) with the recent FDA approval of two robotic-assisted bronchoscopy systems (RBS): the Monarch Platform from Auris Health (2018) and the Ion system from Intuitive Surgical (2019). Small pilot studies of 15 (Monarch) and 29 (Ion) subjects, respectively, demonstrated safety and feasibility of biopsy and diagnosis of PLL using RBS (Rojas-Solano, et al. *J Bronchol Intervent Pulmonol.* 2018;25:168; Fielding et al. *Respiration.* 2019;98[2]:142). While these studies were not powered to evaluate diagnostic yield, they suggested the potential for improved yields over current technologies.

Current bronchoscopic modalities for diagnosis of PLL include electromagnetic navigation bronchoscopy, radial endobronchial ultrasound, and fluoroscopic guidance, all of which have favorable safety profiles but have been plagued by a wide range in diagnostic yields (38% to 88%) (Eberhardt R, et al. *Am J Respir Crit Med.* 2007;176[1]:36; Ost DE, et al. *Am J Respir Crit Care Med.* 2016;193[1]:68). Despite the discordant history of efficacy of PLL sam-

pling modalities, they have gained widespread adoption due to the increasing need to access the periphery. That said, many operators have been left wanting, making new technologies attractive options despite a lack of data. The emergence of RBS may present an opportunity to change the way we approach bronchoscopic procedures, making what was a manual procedure into one that is machine-assisted and, perhaps, improving our accuracy of repetition. The robotic age of lung medicine is an exciting proposition, however, it is paramount that we pursue a robust evidence-based strategy with multicentered clinical trials and move beyond the limitations of registry data in order to carefully embrace these new technologies.

Christina MacRosty, DO
Incoming Fellow-in-Training Member
Jason Akulian, MD, MPH, FCCP
Steering Committee Member

Pediatric Chest Medicine

PARDS: A new definition
Pediatric Acute Respiratory Distress Syndrome (PARDS) is a multifactorial clinical syndrome associated with high morbidity and mortality in children. It is caused by disruption of the alveolar epithelial-endothelial permeability barrier leading to accumulation of protein-rich fluid in the alveoli and surfactant degradation. These changes result in a restrictive lung disease charac-

terized by hypoxemia, radiographic opacities, decreased FRC, and lung compliance and increased physiologic dead space. Resolution usually occurs after several weeks, with



Dr. Rao

potential development of fibrosis. The most common cause of ARDS in children is viral respiratory infection, although associated with many underlying conditions, including pneumonia, sepsis, trauma, burns, pancreatitis, inhalation, transfusion, and cardiopulmonary bypass.

In 2015, an international panel of experts convened the Pediatric Acute Lung Injury Consensus Conference (PALICC) to establish new definitions and guidelines for PARDS. The 2015 PALICC definition broadens to include any new parenchymal infiltrate(s) and allows use of pulse oximetry to avoid underestimating ARDS prevalence in children. It also allows utilization of the oxygenation index (OI) and oxygenation saturation index (OSI) rather than the PaO₂/Fio₂ (P/F) ratio to assess hypoxemia (PARDS: consensus. *Pediatr Crit Care Med.* 2015;16[5]:428; Orloff et al. *Pediatr Allergy Immunol Pulmonol.* 2019;32[2]:35).

In a follow-up international, pro-

spective, cross-sectional, observational study across 27 countries, the PALICC definition identified more children as having PARDS than the Berlin definition. The PALICC PARDS severity groupings improved mortality risk stratification. The PALICC PARDS framework appears to be a better tool for future epidemiologic and therapeutic research among children with PARDS (Khemani et al. *Lancet Respir Med.* 2019;7[2]:115).

Harish Rao, MD
Steering Committee Member

EIGHT* people have died! Need action now

Pediatricians nationwide have raised the alarm as the numbers of middle- and high-school students who are vaping continues to skyrocket. The National Youth Tobacco survey (2018) showed a 78% increase in e-cigarette use in high school students with a 48% increase in middle school students between 2017-2018. Now considered a public health crisis with hundreds of cases of severe respiratory illnesses and eight deaths linked to vaping, our physicians, legislators, educators, and respiratory health organizations are joining forces to curb its use in adolescents.

The American College of Chest Physicians has long supported regulation of e-cigarettes, joining the Forum of International Respiratory Societies in a position statement

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ciated with increased mortality. Patients with a progressive fibrotic ILD have similar mortality rates to those with IPF (Adegunsoye, et al. *Ann Am Thorac Soc.* 2019 May;16[5]:580). The ability to correlate radiographic findings with mortality could potentially become an important marker of clinical deterioration, especially in those patients who are unable to perform PFTs. In addition, it can also be beneficial in those with co-existent emphysema, since PFTs may be confounded by this overlap. Nakagawa and colleagues proposed a computer-aided method for qCT analysis of honeycombing in patients with IPF. The algorithm for the qCT analysis also has specific parameters to exclude emphysematous lesions on imaging. The %honeycomb area (HA) was correlated with a composite physiologic index derived from PFTs (calculated from FEV₁, FVC and DLCO). This tool can accurately quantify the percentage of honeycombing and aid in monitoring IPF. Using this protocol, Nakagawa was able to demonstrate

a significant correlation with 3-year mortality, with a marked difference found when using a cutoff value of 4.8% (Nakagawa, et al. *Plos One.* 2019 Mar; 14[3]:e0214278). Furthermore, patient survival in IPF has been compared against the CALIPER program and PFTs. Mortality for patients was significantly associated with pulmonary vessel volume (PVV), an innovative tool that quantified the volume of the pulmonary artery and veins, which may become a new parameter used for disease monitoring. Using qCT in addition to PFTs provides more tangible evidence to help monitor patients with IPF, guide treatment decisions, and plan for transplant or palliative care. The growing use of PVV in qCT has yet to be fully elucidated, but it does have a promising role (Jacob, et al. *Eur Respir J.* 2017;49[1]. doi: 10.1183/13993003.01011-2016).

Despite the positive outlook for qCT, there are major issues that limit its widespread use. During the image acquisition process, there is a lack of consistency and quality control, stemming from

multiple different manufacturers of CT scan machines, reconstitution methods, radiation doses, and noise or inspiratory efforts of patients. The Radiologic Society of North America (RSNA) is attempting to fix this issue by creating a standardized protocol for collecting images used for qCT (Castillo-Saldana, et al. *J Thorac Imaging.* 2019 Aug 7. doi: 10.1097/RTI.0000000000000440). In order to move forward with adaptation of qCT, a standardized approach and handling of images needs to be created.

Quantitative CT is an exciting new prospect for the care of patients with ILD. As these patients, and their management, become more complex, expanding the toolbox for physicians is much needed. It will be fascinating to see how the role of qCT takes shape over the coming years.

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recommending bans on flavored e-cigarettes and restricting use in areas where children are present.

The Administration announced this week its intention to “clear the market” of all flavored e-cigarettes. Sweet and fruit flavorings are known to entice adolescents to try e-cigarettes while the variety and ability to choose their own combina-



Dr. Cataletto

tions of flavors continues to bring teens back again and again. We know that the brain continues to develop into our mid-twenties, causing teens to be more vulnerable to the addictive properties of nicotine.

Increasing numbers of exposures in adolescents and the severity of vaping-related illnesses have prompted states to take a proactive approach to keep e-cigarettes out of the hands of children. Michigan was the first state to ban the sale of flavored e-cigarettes online and in brick and mortar stores with compliance to take effect within the next 30 days. Other states are expected to follow suit.

Legislation is an important step in our efforts to curb vaping and protect our children.

Mary Cataletto MD, FAAP, FCCP
NetWork Chair

*As the vaping statistics are changing daily, the reported numbers in this report are as of September 20, 2019.

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Pulmonary Physiology, Function, and Rehabilitation Pulmonary rehab and COPD

The introduction of pulmonary rehabilitation (PR) into the care of a patient with COPD can be a life-changing intervention. It has not only been shown to significantly improve symptoms, daily function, and quality of life – but also reduce the risk



Dr. Gartman

of acute exacerbation (Spruit et al. *Am J Respir Crit Care Med.* 2013;188[8]:e13).

However, the referral rate for PR is extremely low, and many patients with COPD, despite having high symptom burdens, may be unaware of its existence.

Unfortunately, this problem is worsened by PR program availability and proximity, with recent estimates suggesting that there are only 831 PR centers in the US for 24 million patients with COPD (Bhatt. *Ann Am Thorac Soc.* 2019;16[1]:55).

As a result, there is an immediate need to explore alternative strategies that enable patients to realize the benefits of PR outside of a facility-based program (Rochester, et al. *Am J Respir Crit Care Med.* 2015;192[11]:1373).

Recently, there have been many proposals for adapting PR programs to accommodate the maximum number of participants; these have included home-, telehealth- or internet-based programs, and low-impact exercise (eg, yoga or tai-chi) regimens.

While these interventions may benefit our patients with COPD, current data do not support that they are a replacement for or replicate the robust outcomes of a formal PR program. It is important that in the process of expanding the availability of “pulmonary rehab,” we do not dilute the process as to limit its returns. Significant attention is being paid to developing novel program designs that utilize technology and nonfacility-based programs – and in the end, there will be a balance struck between beneficial outcomes, program personalization, and proper patient selection for a given regimen.

Eric Gartman, MD, FCCP
Steering Committee Member

Thoracic Oncology A new era in lung cancer diagnostics: Robotic-assisted bronchoscopy

Lung cancer screening leads to increased detection of early stage lung cancer (LC). The majority of nodules detected are peripherally located.



Dr. Patel

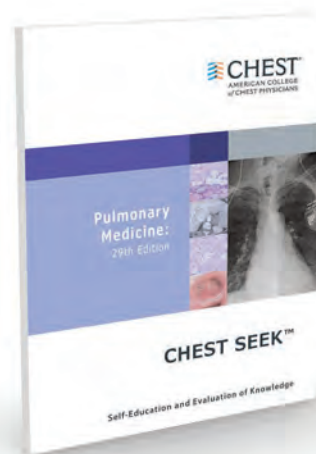
Image-guided bronchoscopic modalities, including radial probe endobronchial ultrasound (r-EBUS) and electromagnetic navigation bronchoscopy (ENB), allow diagnosis of peripheral nodules with a low rate of complications. Although a meta-analysis of image-guided bronchoscopic procedures reported a diagnostic yield of 70% (Wang Memoli JS, et al. *Chest.* 2012;142[2]:385), the diagnostic yield remains inferior to CT-guided biopsy. Robotic-assisted bronchoscopy (RAB) with four-way steering, 180 degrees of deflection in any direction, and better access to peripheral airways may improve the diagnostic yield. Two FDA-ap-

proved platforms are commercially available. The Monarch System, (Auris Health) has a 3.2-mm outer diameter and a 1.2-mm working channel. Results from an ongoing prospective, multicenter study in 24 patients revealed successful localization of targeted lesions in 92%, with no significant adverse events (Chen, et al. *Am J Respir Crit Care Med.* 2019;199:A7304/NCT03727425; Clinical Trials. 2019. <https://clinicaltrials.gov/ct2/show/NCT03727425>).

The Ion Endoluminal System (Intuitive Surgical) has a 3.5-mm outer diameter and a 2.0-mm working channel. Preliminary data revealed 96.6% of target lesions were successfully reached, and no adverse events (Fielding et al. *Chest.* 2017;152[4]:A858). A prospective, multicenter randomized trial is currently ongoing (Clinical Trials. 2019. <https://clinicaltrials.gov/ct2/show/NCT03893539>).

The aim of bronchoscopic procedures is to safely and effectively diagnose early stage LC. RAB shows a great deal of potential in the future of LC diagnostics.

Priya Patel, MD
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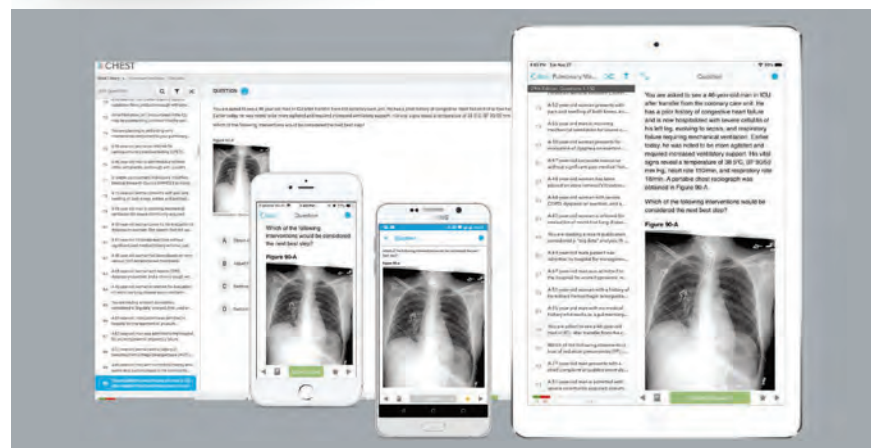


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