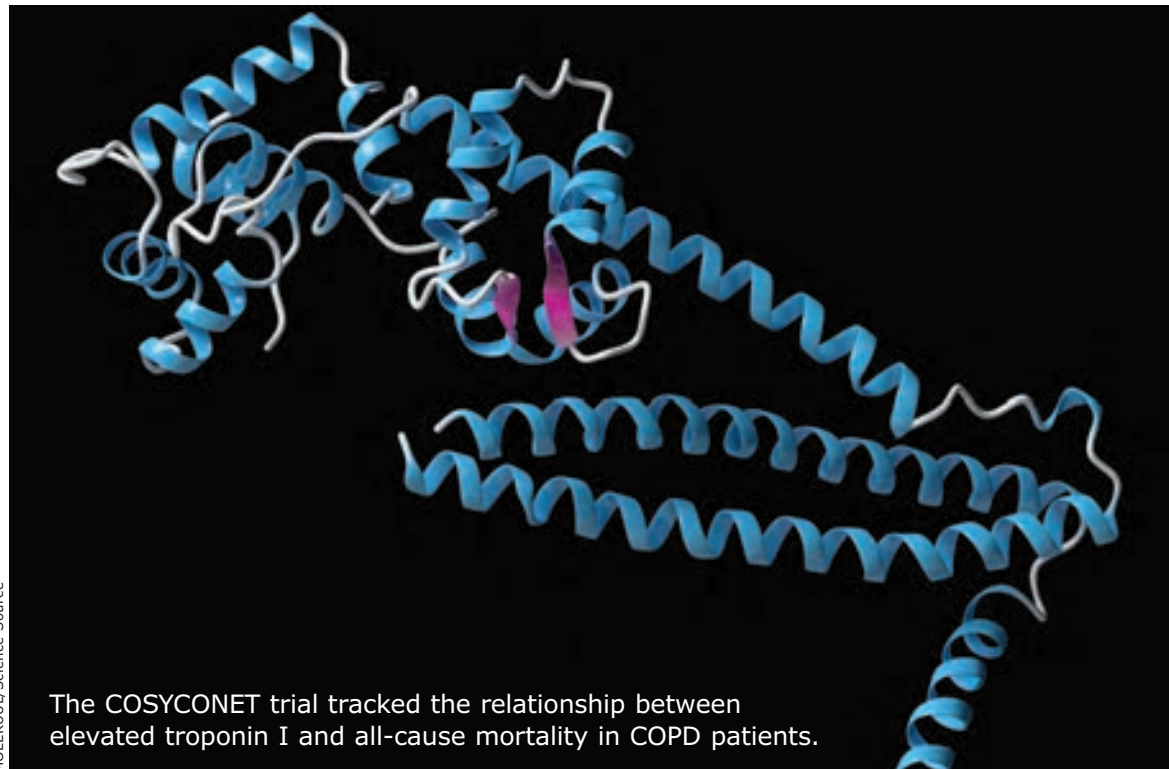




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The COSYCONET trial tracked the relationship between elevated troponin I and all-cause mortality in COPD patients.

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Troponin I: Powerful all-cause mortality risk marker in COPD

BY TED BOSWORTH

MDedge News

PARIS – High troponin I concentrations in the blood of patients with chronic obstructive pulmonary disease (COPD) has been found to be a remarkably powerful predictor of all-cause mortality even after researchers adjusted for all major cardiovascular and COPD prognostic indicators, according to a late-breaker presentation at the annual congress of the European Respiratory Society.

Troponin I is detectable in the plasma of most patients with COPD, but relative increases in troponin I correlate with greater relative increases in most cardiovascular and COPD risk

factors, according to Benjamin Waschki, MD, Pulmonary Research Institute, LungenClinic, Grosshansdorf, Germany.

The relationship between increased troponin I and increased all-cause mortality was observed in an ongoing prospective multicenter cohort of COPD patients followed at 31 centers in Germany. The cohort is called COSYCONET and it began in 2010. The current analysis evaluated 2,020 COPD patients without regard to stage of disease.

There were 136 deaths over the course of follow-up. Without adjustment, the hazard ratio for death was more than twofold higher in the highest quartile of troponin I (equal to or greater

TROPONIN // *continued on page 7*

Physician burnout may jeopardize patient care

BY JEFF CRAVEN

MDedge News

Physicians experiencing burnout are twice as likely to be associated with patient safety issues and deliver a lower quality of care from low professionalism and are three times as likely to be rated poorly among patients because of depersonalization of care, according to recent research published in *JAMA Internal Medicine*.

“The primary conclusion of this review is that physician burnout might jeopardize patient care,” Maria Panagioti, PhD, from the National Institute for Health Research (NIHR) School for Primary Care Research and the NIHR Greater Manchester Patient Safety Translational Research Centre at the University of Manchester (England) and her colleagues wrote in their study. “Physician wellness and quality of patient care are critical [as are] complementary dimensions of health care organization efficiency.”

Dr. Panagioti and her colleagues performed a search of the MEDLINE, EMBASE, CINAHL, and PsycInfo databases and found 47 eligible studies on the topics of physician burnout and

BURNOUT // *continued on page 10*

INSIDE HIGHLIGHT



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UN aims to eradicate TB by 2030

BY KARI OAKES

MDedge News

A concerted international effort is planned to eradicate tuberculosis, a lethal disease

affecting one-quarter of the world's population by the year 2030.

On Sept. 26, 2018, the United Nations General Assembly convened a high-level meeting of global stakeholders to solidify the eradication

plan, addressing the global crisis of tuberculosis, the world's most deadly infectious disease.

"We must seize the moment," said Tereza Kasaeva, MD, director of the World Health Organization's

global TB program, speaking at a telebriefing and press conference accompanying the release of the World Health Organization's annual global tuberculosis report. "It's unacceptable in the 21st century that millions

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lose their lives to this preventable and curable disease.”

Tuberculosis caused 1.6 million deaths globally in 2017, and the World Health Organization (WHO) estimates that, of the 10 million new cases of TB last year, 558,000 are multi-drug resistant (MDR) infections.

Though death rates and new cases

are falling globally each year, significantly more resources are needed to boost access to preventive treatment for latent TB infection; “most people needing it are not yet accessing care,” according to the press briefing accompanying the report.

A review and commentary on TB incubation and latency published in *BMJ* (2018;362:k2738 doi:

10.1136/bmj.k2738; e-pub 23 Aug 2018) has called into question the focus on preventive treatment of latent cases at the expense of reaching those most likely to die from TB (e.g., HIV patients, children of individuals living with active TB). The authors state that “latent” TB is identified by indirect evidence of present or past infection with *My-*

cobacterium tuberculosis as inferred by a detectable adaptive immune response to *M. tuberculosis* antigens. Active TB infection is overwhelmingly the result of a primary infection and almost always occurs within 2 years.

For the ambitious goal of TB eradication by the year 2030, treatment coverage must rise to 90% globally from the current 64%, according to the report.

Progress in southern Africa and in the Russian Federation, where efforts have led to a 30% reduction in TB mortality and a decrease in incidence of 5% per year, show that steep reductions in TB are possible when resources are brought to bear on the problem, said Dr. Kasaeva. “We should acknowledge that actions in some countries and regions show that progress can accelerate,” she said. Still, she noted, “Four thousand lives per day are lost to TB. Tuberculosis is the leading killer of people living with HIV, and the major cause of deaths related to antimicrobial resistance” at a global level.

Two thirds of all TB cases occur in eight countries, with China, India, and Indonesia leading this group. About half of the cases of MDR TB occur in China, India, and Russia, said Dr. Kasaeva, and globally only one in four individuals with MDR TB who need access to treatment have received it. “We need to urgently tackle the multidrug resistant TB public health crisis,” she said.

Major impediments to successful public health efforts against TB are underdiagnosis and underreporting: It is estimated that 3.6 million of 2017’s 10 million new cases were not officially recorded or reported. Countries where these problems are most serious include India, Indonesia, and Nigeria. Fewer than half of the children with TB are reported globally, according to the report.

People living with HIV/AIDS and infected with TB number nearly 1,000,000, but only about half of these were officially reported in 2017.

In terms of prevention priorities, WHO has recommended targeting treatment of latent TB in two groups: people living with HIV/AIDS, and children under the age of 5 years who live in households with TB-infected individuals.

“To enable these actions,” said Dr. Kasaeva, “we need strengthened commitments not just for TB care, but for overall health services. So the aim for universal coverage is real.” Underreporting is particularly prevalent in lower income countries with large unregulated private sec-

Continued on following page

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tors, she said, though India and Indonesia have taken corrective steps to increase reporting.

A meaningful global initiative will not come cheap: The current annual shortfall in funding for TB prevention, diagnosis, and treatment is about \$3.5 billion. By the year 2022, the gap between funding and what's needed to stay on track for the 2030 target will be over \$6 billion, said Dr. Kasaeva.

The best use of increased resources for TB eradication will be in locally focused efforts, said Irene Koek, MD, the United States Agency for International Development's deputy administrator for global health. "It is likely that each region requires a tailored response." Further, "to improve quality of care we need to ensure that services are patient centered," she said at the press conference.

To that end, Dr. Koek expects that at the upcoming high-level meeting, the United Nations member states will be called on to develop an open framework, with clear accountability for monitoring and reviewing progress. The road forward should "celebrate accomplishments and acknowledge shortcomings," she said. Some recent studies have shown that treatment success rates above 80% for patients with MDR TB can be achieved.

"Lessons learned from these experiences should be documented and shared in order to replicate success globally," said Dr. Koek.

The United States, said Dr. Koek, is the leading global investor in TB research and treatment. "We welcome increased partnerships, especially with countries with the highest burden, to end global suffering from this disease."

Eric Goosby, MD, the United Nations special envoy on TB, used his speaking time to lend some perspective to the social framework around TB's longtime lethality.

There are aspects of TB infection that differentiate it from HIV/AIDS, said Dr. Goosby, who has spent most of his clinical and public health career on HIV/AIDS treatment and prevention. In contrast to an infection that at present requires a lifetime of treatment, TB can ordinarily be treated in 6 months, making it an unpleasant episode that an individual may be eager to move past. Additionally, the fact that TB has had a "hold on the world since the time of the ancient Egyptians" may paradoxically have served to lessen urgency in research and treatment efforts, he noted.

Dr. Goosby also spoke of the stig-

ma surrounding TB, whose sufferers are likely to be facing dire poverty, malnutrition, and other infectious disease burdens. Civil society concerned with TB, he said, has spoken up "for those without a voice, for those who have difficulty advocating for themselves."

Dr. Kasaeva agreed, noting that TB "affects the poorest of the poor, which makes it extraordinarily difficult for activism to come from that population."

However, others have spoken for those affected, said Dr. Goosby. "The TB civil society has put its heart and soul this last year into gathering political will from leaders around the world. ... It's not a passive effort; it involves a lot of work." During the past year of concerted effort, he said, "All of us have known the difficulty of pushing a political leader up that learning curve."

As the upcoming high-level meeting approaches, those who have been working on the effort can feel the momentum, said Dr. Goosby. Still, he noted, "While there's a significant step forward, this is not the time for a victory dance. This is really the time for a reflection. ... Do we understand the burden in our respective countries, and has the response been adequate?"

The goal for the high-level meeting is to have leaders "step up to commit, not for one day, or for one meeting, but for the duration of the effort," said Dr. Goosby. "We must make sure that the words that we hear next week from our leaders translate into action. ... Next week the world will say, 'No more. No longer. No one is immune to TB. Tuberculosis is preventable; tuberculosis is treatable; tuberculosis is curable.'"

The BMJ commentary, by Marcel A. Behr, MD, of McGill International TB Centre, Infectious Diseases and Immunity in Global Health Program, McGill University Health Centre Research Institute, Montreal, and his colleagues, recommended caution when building a prevention strategy around treating many millions of individuals with "latent" TB. They wrote, "Immunoreactivity to TB does not necessarily indicate the presence of live bacteria, as reactivity can persist after infection has been cleared. Classifying two billion people with evidence of immunoreactivity as having latent TB infection may divert fundamental research and public health interventions away from transmissible active TB disease and newly infected people at highest risk of progression to disease."

koakes@mdedge.com

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

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Prognostic ability of recommended tests affirmed in prostanoid-treated PAH

BY WILL PASS

MDedge News

FROM THE JOURNAL CHEST® ■ The results of guideline-recommended prognostic tests that measure mortality risk in patients with pulmonary arterial hypertension (PAH) are strongly associated with survival in those who are receiving a parenteral prostanoid, according to a recent study.

Patients with no lower-risk findings or at least two higher-risk findings had the worst outcomes, reported lead author Sonja Bartolome, MD, of the University of Texas Southwestern Medical Center in Dallas, and her colleagues.

Prostanoids are the most effective therapy for advanced PAH. However, patients may respond inadequately, so guidelines recommend lung transplant evaluation 3 months after starting a prostanoid.

The current study relied upon the 2015 European Society of Cardiology and European Respiratory Society (ESC/ERS) consensus guidelines. The guidelines recommend several tests to determine adequate response to therapy, including invasive

hemodynamic measures, brain natriuretic peptide (BNP) level, N-terminal BNP (NT-proBNP) level, 6-minute walk distance (6MWD), and functional class (FC). Results of these tests are sorted into three hazard ratios for mortality: lower, intermediate, or higher risk.

It is commonly accepted that these risk categories can predict survival. For example, a patient with several higher-risk results and no lower-risk results would have a poor prognosis. However, the reliability of this method is poorly studied.

“In practicality the definition of an ‘inadequate response’ remains nebulous given that data on prognostic markers in patients on advanced therapy is limited,” the authors wrote. Their report was published in CHEST®. “We therefore sought to evaluate whether consensus guidelines recommended prognostic measures associate with survival free from transplant in PAH patients initiating parenteral prostanoids.”

The retrospective study involved 195 patients with group 1 PAH at multiple treatment centers who received a parenteral prostanoid between 2007 and 2016. Diagnosis

relied upon CT angiography, ventilation-perfusion scan, pulmonary function testing, cardiac catheterization, or echocardiogram. Eligible diagnoses were idiopathic PAH (n = 111), heritable PAH (n = 9), and PAH associated with connective tissue disease (n = 61), congenital heart disease (n = 12), and HIV (n = 2).

Patients received either IV epoprostenol (n = 132), SC treprostinil (n = 38), or IV treprostinil (n = 25). Routine prognostic testing was done prior to prostanoid therapy, and again at least 90 days later (with right heart catheterization). The investigators then analyzed the data for associations between test outcomes and survival. Results showed that survival rates at 1, 2, and 3 years were 84%, 77%, and 67%, respectively. All major prognostic measures improved after patients started a prostanoid. Better SVO₂, BNP, NT-proBNP, 6MWD, and FC were associated with survival, but cardiac index (CI) was not. Survival was least likely in patients who had at least two higher-risk measures or no lower-risk measures; of these patients, less than 50% were alive after 2 years.

“These findings are likely broadly applicable to PAH patients being

treated with parenteral prostanoids,” the authors wrote, citing the fact that all patients in the study were newly started on either of the two parenteral prostanoids currently available in the United States (including patients who were treatment naive as well as those transitioning to parenteral therapy) and the study involved patients with multiple PAH subtypes. However, not all of the prognostic measures were reliable, particularly CI. Although CI is used as a major determinant for lung transplant, the authors noted that the lack of association between CI and survival suggests that “the strength and usefulness of some individual prognostic measures may differ for prostanoid-treated PAH patients.” Some of the authors disclosed financial ties to United Therapeutics, which markets treprostinil for infusion (Remodulin), and Actelion, which markets epoprostenol for injection (Veletri), as well as other pharmaceutical companies.

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SOURCE: Bartolome S et al. Chest. 2018 Sep 1. doi: 10.1016/j.chest.2018.03.050.

Troponin may indicate risk in other chronic diseases // continued from page 1

than 6.6 ng/mL), when compared with the lowest (under 2.5 ng/mL) (HR, 2.42; *P* less than .001). Graphically, the mortality curves for each of the quartiles began to separate at about 12 months, widening in a stepwise manner for greater likelihood of death from the lowest to highest quartiles.

The risk of death from any cause remained elevated for the highest relative to lowest troponin I quartiles after adjusting for cardiovascular risk factors and after adjusting for COPD severity. Again, there was a distinct stepwise separation of the mortality curves for each higher troponin quartile.

Of particular importance, troponin I remained predictive beyond the BODE index, which is a currently employed prognostic mortality predictor in COPD, according to Dr. Waschki. When elevated troponin is defined as greater than 6 ng/mL and a high BODE score as greater than 4, mortality was higher for those with a high BODE and low troponin than a high troponin and low BODE (*P* less than .001), but a high troponin I was associated with a higher risk of mortality when BODE was low (*P* less than .001). Moreover, when both troponin I and BODE were elevated, all-cause mortality was more than doubled, relative to those without either risk factor (HR, 2.56; *P* = .003), Dr. Waschki reported.

After researchers adjusted for major cardiovascular risk factors, such as history of MI and renal impairment, and for major COPD risk factors, such as 6-minute walk test and BODE index, those in the highest quartile had a more than 50% greater risk of death relative to those in

The mortality curves for each of the quartiles began to separate at about 12 months, widening in a stepwise manner for greater likelihood of death.

the lower quartile over the 3 years of follow-up (HR, 1.69; *P* = .007), according to Dr. Waschki.

Although troponin I is best known for its diagnostic role in MI, it is now being evaluated as a risk stratifier for many chronic diseases, such as heart failure and chronic kidney disease, explained Dr. Waschki in providing background for this study. He reported that many groups are looking at this as a marker of risk in a variety of chronic diseases (see story on p. 48).

In fact, a group working independently published a study in COPD just weeks before the ERS Congress that was complementary to those presented by Dr. Waschki. In this study, the goal was to evaluate troponin I as a predictor of cardiovas-

cular events and cardiovascular death (Adamson PD et al. J Am Coll Cardiol. 2018;72:1126-37). Performed as a subgroup analysis of 1,599 COPD patients participating in a large treatment trial, there was an almost fourfold increase in the risk of cardiovascular events (HR, 3.7; *P* = .012) when those in the highest quintile of troponin I (greater than 7.7 ng/mL) were compared with those in the lowest quintile (less than 2.3 ng/mL).

When compared for cardiovascular death, the highest quintile, relative to the lowest quintile, had a more than 20-fold increased risk of cardiovascular death (HR 20.1; *P* = .005). In the Adamson et al. study, which evaluated inhaled therapies for COPD, treatment response had no impact on troponin I levels or on the risk of cardiovascular events or death.

Based on this study and his own data, Dr. Waschki believes troponin I, which is readily ordered laboratory value, appears to be a useful tool for identifying COPD patients at high risk of death.

“The major message is that, after adjusting for all known COPD and cardiovascular risk factors, troponin I remains a significant independent predictor of mortality,” he said.

Dr. Waschki reports no relevant conflicts of interest.

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Registry documents benefits of bronchial thermoplasty in asthma patients

BY TED BOSWORTH

MDedge News

PARIS – A global registry to track the safety and efficacy of bronchial thermoplasty for the treatment of severe asthma shows benefits comparable to those previously reported in randomized trials, according to 1-year results presented at the annual congress of the European Respiratory Society.

Bronchothermoplasty has been Food and Drug Administration approved since 2010, but joint 2014 guidelines from the ERS and the American Thoracic Society recommended that this procedure be restricted to patients participating in a registry, making these findings an important part of an ongoing assessment, according to Alfons Torrego Fernandez, MD, of the pulmonology service at Hospital de la Santa Creu i Sant Pau, Barcelona.

The BT Global Registry (BTGR), created at the end of 2014, involves 18 centers in Australia, Europe, and



Dr. Alfons Torrego Fernandez

South Africa. Dr. Fernandez provided data on 123 of the 157 patients enrolled by the end of 2016. All had at least 1 year of follow-up.

Compared with the year prior to bronchial thermoplasty, the proportion of patients with severe exacerbations in the year following this procedure fell from 90.3% to 59.6%, a 34% reduction (P less than .001).

The proportion of patients requiring

oral corticosteroids fell from 47.8% to 23.5%, a reduction of more than 50%.

Relative to the year prior to bronchial thermoplasty, “there was also a reduction in emergency room visits [21.1% vs. 54.6%] and hospitalizations [20.2% vs. 43%] as well as a reduction in the need for asthma maintenance medications,” Dr. Fernandez reported.

On the Asthma Control Questionnaire (ACQ), quality of life (QOL) was improved on average by 1.2 points from the prior year (4.48 vs. 3.26; P less than .05), according to Dr. Fernandez. The proportion of patients who achieved at least a 0.5-point increase in the ACQ, a level that Dr. Fernandez said is considered clinically relevant, was 67.1%.

However, when lung function measures such as forced expiratory volume in 1 second and fractional exhaled nitric oxide taken 1 year after bronchothermoplasty were compared with the same measures taken prior to this treatment, there was no significant improvement, he said.

Bronchial thermoplasty involves the use of thermal energy delivered through a bronchoscope to reduce airway smooth muscle mass, thereby eliminating a source of airway restriction. Although nearly 70% of severe asthma patients in this BTGR derived an improvement in quality of life, 30% did not. Asked if the registry has provided any insight about who does or does not respond, Dr. Fernandez acknowledged that this is “the key question,” but added that “no specific profile or biomarker” has yet been identified.

Although the technical aspects of bronchial thermoplasty “are quite well standardized,” Dr. Fernandez acknowledged that there might be a learning curve that favors experienced operators. He reported that outcomes between high- and low-volume centers in BTGR have not yet been compared. Dr. Fernandez reported having no conflicts of interest. The registry is funded by Boston Scientific.

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Azithromycin for COPD exacerbations cut ICU admissions

BY TED BOSWORTH

MDedge News

PARIS – In patients with a chronic obstructive pulmonary disease (COPD) exacerbation, initiating azithromycin at the time of hospitalization provided improvement in a variety of outcomes at 90 days, including risk of death, according to a placebo-controlled trial presented as a late-breaker at the annual congress of the European Respiratory Society.

In patients with COPD, “azithromycin initiated in the acute setting and continued for 3 months appears to be safe and potentially effective,” reported Wim Janssens, MD, PhD, division of respiratory medicine, University Hospital, Leuven, Belgium.

The phrase “potentially effective” was used because the primary endpoint, which was time to treatment failure, fell just short of statistical significance ($P = .053$), but the rate of treatment failures, which was a coprimary endpoint ($P = .04$), and all of the secondary endpoints, including mortality at 90 days ($P = .027$), need for treatment intensification ($P = .02$), and need for an intensive care unit (ICU) admission ($P = .003$), were significantly lower in the group receiving azithromycin rather than placebo.

In a previous trial, chronic azithromycin therapy on top of usual care in patients frequently hospitalized for COPD was associated with a reduction in the risk of exacerbations and an improvement in quality of life (N Engl J Med. 2011;365:689-98). However, Dr. Janssens explained that this strategy

is not commonly used because it was associated with a variety of adverse events, not least of which was QTc prolongation.

The study at the meeting, called the BACE trial, was designed to test whether azithromycin could be employed in a more targeted approach to control exacerbations. In the study, 301 COPD patients hospitalized with an acute exacerbation were randomized within 48 hours of admission to azithromycin or placebo. For the first 3 days, azithromycin was administered in a 500-mg dose. Thereafter, the dose was 250 mg every second day. Treatment was stopped at 90 days.

The primary outcome was time to treatment failure, a novel composite endpoint of any of three events: the need for treatment intensification, the need for step-up hospital care (either ICU admission or hospital readmission), or death by any cause. The two treatment arms were also compared for safety, including QTc prolongation.

The treatment failure rates were 49% in the azithromycin arm and 60% in the placebo arm, producing a hazard ratio of 0.73. Although this outcome fell short of significance, Dr. Janssens suggested that benefits over the 90 days of treatment are support-



Dr. Wim Janssens

ed by the secondary outcomes. However, he also cautioned that most relative advantages for azithromycin over placebo were found to dissipate over time.

“The maximum separation between the azithromycin and placebo arms [for the primary outcome] occurred at 120 days or 30 days after the medication was stopped,” Dr. Janssens reported. After this point, the two arms converged and eventually overlapped.

However, the acute benefits appeared to be substantial. For example, average hospital stay

over the 90-day treatment period was reduced from 40 to 10 days ($P = .0061$), and the ICU days fell from 11 days to 3 days in the azithromycin relative to the placebo group. According to Dr. Janssens, the difference in hospital stay carries “important health economic potential that deserves further attention.”

Of the three QTc events that occurred during the course of the study, one was observed in the placebo group. There was no significant difference in this or other adverse events, according to Dr. Janssens.

Dr. Janssens reports no conflicts of interest relevant to this study.

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patient care, which altogether included data from a pooled cohort of 42,473 physicians. The physicians were median 38 years old, with 44.7% of studies looking at physicians in residency or early career (up to 5 years post residency) and 55.3% of studies examining experienced physicians. The meta-analysis also evaluated physicians in a hospital setting (63.8%), primary care (13.8%), and across various different health care settings (8.5%).

The researchers found physicians with burnout were significantly associated with higher rates of patient safety issues (odds ratio, 1.96; 95% confidence interval, 1.59-2.40), reduced patient satisfaction (OR, 2.28; 95% CI, 1.42-3.68), and lower quality of care (OR, 2.31; 95% CI, 1.87-2.85). System-reported instances of patient safety issues and low professionalism were not statistically significant, but the subgroup differences did reach statistical significance (Cohen Q, 8.14; $P = .007$). Among residents and physicians in their early career, there was a greater association between burnout and low professionalism (OR, 3.39; 95% CI, 2.38-4.40), compared with physicians in the middle or later in their career (OR, 1.73; 95% CI, 1.46-2.01; Cohen Q, 7.27; $P = .003$).

“Investments in organizational strategies to jointly monitor and improve physician wellness and patient care outcomes are needed,” Dr. Panagiotti and her colleagues wrote in the study. “Interventions aimed at improving the culture of health care organizations, as well as interventions focused on individual physicians but supported and funded by health care organizations, are beneficial.”



Courtesy National Cancer Institute

Researchers noted the study quality was low to moderate. Variation in outcomes across studies, heterogeneity among studies, potential selection bias by excluding gray literature, and the inability to establish causal links from findings because of the cross-sectional nature of the studies analyzed were potential limitations in the study, they reported.

The study was funded by the United Kingdom NIHR School for Primary Care Research and the NIHR Greater Manchester Patient Safety Translational Research Centre. The authors report no relevant conflicts of interest.

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SOURCE: Panagiotti M et al. JAMA Intern Med. 2018 Sep 4. doi: 10.1001/jamainternmed.2018.3713.

VIEW ON THE NEWS

Quality improvement projects for burnout prevention are needed

Because of a lack of funding for research into burnout and the immediate need for change based on the effect it has on patient care seen in Panagiotti et al., the question of how to address physician burnout should be answered with quality improvement programs aimed at making immediate changes in health care settings, Mark Linzer, MD, wrote in a related editorial.

“Resonating with these concepts, I propose that, for the burnout prevention and wellness field, we encourage quality improvement projects of high standards: multiple sites, concurrent control groups, longitudinal design, and blinding when feasible, with assessment of outcomes and costs,” he wrote. “These studies can point us toward what we will evaluate in larger trials and allow a place for the rapidly developing information base to be viewed and thus become part of the developing science of work conditions, burnout reduction, and the anticipated result on quality and safety.”

There are research questions that have yet to be answered on this topic, he added, such as to what extent do factors

like workflow redesign, use and upkeep of electronic medical records, and chaotic workplaces affect burnout. Further, regulatory environments may play a role, and it is still not known whether reducing burnout among physicians will also reduce burnout among staff. Future studies should also look at how burnout affects trainees and female physicians, he suggested.

“The link between burnout and adverse patient outcomes is stronger, thanks to the work of Panagiotti and colleagues,” Dr. Linzer said. “With close to half of U.S. physicians experiencing symptoms of burnout, more work is needed to understand how to reduce it and what we can expect from doing so.”

Dr. Linzer is from the Hennepin Healthcare Systems in Minneapolis. These comments summarize his editorial regarding the findings of Panagiotti et al. He reported support for Wellness Champion training by the American College of Physicians and the Association of Chiefs and Leaders in General Internal Medicine and that he has received support for American Medical Association research projects.

NEWS

Disruptive physicians: Is this an HR or MEC issue?

BY ALICIA GALLEGOS

MDedge News

Disruptive physician behavior can be more than a headache for the medical team, it can greatly lower staff morale and compromise patient care. Addressing this behavior head-on is imperative, experts said, but knowing which route to take is not always clear.

Physician leaders may wonder: When is this a human resources (HR) issue and when should the medical executive committee (MEC) step in?



MR. PETERS

The answer depends on the circumstances and the employment status of the physician in question, said Mark Peters, a labor and employment attorney based in Nashville, Tenn.



MR. MOSELEY

“There are a couple of different considerations when deciding how, or more accurately who, should address disruptive physician behavior in the workplace,” Mr. Peters said in an interview. “The first consideration is whether the physician is employed by the health care entity or is a contractor. Typically, absent an employment relationship with the physician, human resources is

not involved directly with the physician and the issue is handled through the MEC.”

However, in some cases both HR and the MEC may become involved. For instance, if the complaint is made by an employee, HR would likely get involved – regardless of whether the disruptive physician is a contractor – because employers have a legal duty to ensure a “hostile-free environment,” Mr. Peters said.

The hospital may also ask that the MEC intervene to ensure the medical staff understands all of the facts and can weigh in on whether the doctor is being treated fairly by the hospital, he said.

There are a range of advantages and disadvantages to each resolution path, said Jeffrey Moseley, a health law attorney based in Franklin, Tenn. The HR route usually means dealing with a single point person and typically the issue is resolved more swiftly. Going through the MEC, on the other hand, often takes months. The MEC path also means more people will be involved, and it’s possible the case may become more political, depending on the culture of the MEC.

Continued on following page

Declining lung function linked to heart failure, stroke

BY ANDREW D. BOWSER

MDedge News

Rapid declines in spirometric measures of lung function were associated with higher risks of cardiovascular disease, according to a recent analysis of a large, prospective cohort study.

Rapid declines in forced expiratory volume in 1 second (FEV₁) were as-

The risk of incident heart failure among FEV₁ rapid decliners was particularly high, with a fourfold increase within 12 months.

sociated with increased incidence of heart failure, stroke, and death in the analysis of the ARIC (Atherosclerosis Risk in Communities) study.

The ARIC is a prospective epidemiologic study conducted in four U.S. communities. ARIC was designed to investigate the etiology and natural history of atherosclerotic diseases, and variation in cardiovascular risk factors, medical care, and disease by race, gender, location, and date.

The risk of incident heart failure among FEV₁ rapid decliners was particularly high, with a fourfold increase within 12 months. That suggests clinicians should carefully consider incipient heart failure in patients with rapid changes in FEV₁, investigators reported in the *Journal of the American College of Cardiology*.

Rapid declines in forced vital capacity (FVC) were also associated with higher incidences of heart

failure and death in the analysis by Odilson M. Silvestre, MD, of the division of cardiovascular medicine at Brigham and Women's Hospital, Boston, and colleagues.

The analysis included a total of 10,351 ARIC participants with a mean follow-up of 17 years. All had undergone spirometry at the first study visit between 1987 and 1989, and on the second visit between 1990 and 1992.

One-quarter of participants were classified as FEV₁ rapid decliners, defined by an FEV₁ decrease of at least 1.9% per year. Likewise, one-quarter of participants were classified as FVC rapid decliners, based on an FVC decrease of at least 2.1%.

Rapid decline in FEV₁ was associated with a higher risk of incident heart failure (hazard ratio, 1.17; 95% confidence interval, 1.04-1.33; $P = .010$), and was most prognostic in the first year of follow-up (HR, 4.22; 95% CI, 1.34-13.26; $P = .01$), investigators said.

Rapid decline in FVC was likewise associated with a greater heart failure risk (HR, 1.27; 95% CI, 1.12-1.44; P less than .001).

Increased heart failure risk persisted after excluding patients with incident coronary heart disease in both the FEV₁ and FVC rapid decliners, the investigators said.

A rapid decline in FEV₁ was also associated with a higher stroke risk (HR, 1.25; 95% CI, 1.04-1.50; $P = .015$).

FEV₁ rapid decliners had a higher overall rate of incident cardiovascular disease than those without rapid decline, even after adjustment for baseline variables such as age, sex, race, body mass index, and heart rate (HR, 1.15; 95% CI, 1.04-1.26;

VIEW ON THE NEWS

The latest insight from ARIC

G. Hossein Almassi, MD, FCCP, comments: This is the latest publication from the ARIC study looking at the impact of declining lung function on subsequent incident cardiovascular events. In multiple prior publications from this large observational study, the lowest quartile of FEV₁ and/or FVC was associated with worsening renal function,¹ development of atrial fibrillation,² and heart failure.³ The current study looked at the rate of decline in the FEV₁ and FVC and its effect on incident heart failure, coronary heart disease, and stroke. In concert with prior reports from ARIC, rapid decline in pulmonary function was significantly associated with the cardiovascular events.



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$P = .004$), and FVC rapid decliners likewise had a 19% greater risk of the composite endpoint (HR, 1.19; 95% CI, 1.08-1.32; P less than .001).

The investigators concluded, "Our results provide additional evidence that, in addition to providing information regarding risk of pulmonary disease, serial changes in spirometry also provides the clinician information regarding the risk of [cardiovascular disease]. Our findings also demonstrate that rapid decline in FEV₁ in particular predicts increased risk of incident HF. This risk was particularly high (4-fold increased) within 12 months, suggest-

ing that clinicians should carefully consider incipient HF in patients with rapid changes in FEV₁. Further studies are necessary to determine whether strategies to reduce the rate of decline in FEV₁ and FVC reduce the incidence of [cardiovascular disease]."

The National Heart, Lung, and Blood Institute, the American Heart Association, and other sources supported the study. Dr. Silvestre reported having no relevant conflicts.

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SOURCE: Silvestre OM et al. *J Am Coll Cardiol*. 2018 Sep 4;72(10):1109-22.

Continued from previous page

"If you have to end up taking an action, the employment setting may be a quicker way to address the issue than going through the medical staff side," Mr. Moseley said in an interview. "Most medical staffs, if they were to try to restrict or revoke privileges, they are going to have to go through a fair hearing and appeals, [which] can take 6 months easily. The downside to the employment side is you don't get all the immunities that you get on the medical staff side."

A disruptive physician issue handled by the MEC as a peer review matter or professional review action is protected under the Healthcare Quality Improvement Act, which shields the medical staff and/or hospital from civil damages in the event that they are sued. Additionally, information disclosed during the MEC process that is part of the peer review privilege is confidential

and not necessarily discoverable by plaintiff's attorneys in a subsequent court case.

The way the MEC handles the issue often hinges on the makeup of the committee, Mr. Moseley

The hospital may also ask that the Medical Ethics Committee intervene to ensure the medical staff understands all of the facts and can weigh in on whether the doctor is being treated fairly by the hospital.

noted. In his experience, older medical staffs tend to be more sensitive to the accused physician and question whether the behavior is egregious. Older physicians are generally used to a more "captain

of the ship" leadership style, with the doctor as the authority figure. Younger staffs are generally more sensitive to concerns about a hostile work environment and lean toward a team approach to health care.

"If your leadership on the medical staff is a [group of older doctors] versus a mix of younger docs, they might be more or less receptive to discipline [for] a behavioral issue, based on their worldview," he said.

Disruptive behavior is best avoided by implementing sensitivity training and employing a zero-tolerance policy for unprofessional behavior that applies to all staff members from the highest revenue generators to the lowest, no exceptions, Mr. Peters advised. "A top-down culture that expects and requires professionalism amongst all medical staff [is key]."

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One and done? Single-dose flu antiviral in pipeline

BY BIANCA NOGRADY

MDedge News

A new single-dose influenza antiviral drug appears significantly better than placebo at relieving the symptoms of infection, and reduces viral load faster than does oseltamivir, new research suggests.

Baloxavir marboxil – a selective inhibitor of influenza cap-dependent endonuclease – was tested in two randomized, double-blind, controlled trials. The first was a double-blind, placebo-controlled, dose-ranging, phase 2 randomized trial of 389 Japanese adults aged 20-64 years with acute uncomplicated influenza from December 2015 through March 2016. The second was a phase 3 randomized controlled trial of 1,366 patients comparing baloxavir with placebo and oseltamivir.

The phase 2 study showed patients treated with 10 mg, 20 mg, or 40 mg oral dose of baloxavir experienced a significantly shorter median time to symptom alleviation compared with placebo (54.2, 51, 49.5, and 77.7 hours, respectively), according to a

paper published in the New England Journal of Medicine.

In addition, all three doses showed significantly greater reductions in influenza virus titers on days 2 and 3, compared with placebo.

The phase 3 trial CAPSTONE-1 (NCT02954354) was a double-blind, placebo- and oseltamivir-controlled, randomized trial that enrolled outpatients aged 12-64 years with influenza-like illness in the United States and Japan from December 2016 through March 2017. Patients aged 20-64 years received a single, weight-based oral dose of baloxavir (40 mg for patients weighing more than 80 kg, 80 mg for those weighing 80 kg or less) on day 1 only or oseltamivir at a dose of 75 mg twice daily or matching placebos on a 5-day regimen.

Patients aged 12-19 years were randomly assigned to receive either baloxavir or placebo on day 1 only, according to the researchers.

The median time to alleviation of symptoms was similar in the baloxavir (53.5 hours) and oseltamivir group (53.8 hours). However, patients tak-

VIEW ON THE NEWS

Daniel Ouellette, MD, FCCP, comments: Every flu season I take care of patients in the ICU who have respiratory failure from influenza. Some of these patients die. I remember the 50-year-old man with no past medical illnesses who died after a week of mechanical ventilation. What about the 30-year-old pregnant woman who lived, after being on ECMO for 90 days, losing her baby, and winding up on dialysis? New drugs that will improve clinical outcomes from influenza are needed. Baloxavir may be one of those drugs.

ing baloxavir had significantly faster declines in infectious viral load compared with those taking oseltamivir, which was taken as a 75-mg dose twice daily for 5 days. In addition, patients who were treated with baloxavir within 24 hours of symptom onset showed significantly shorter time to alleviation of symptoms compared with placebo than did those who started treatment more than 24 hours after symptoms began.

Adverse events related to the study drug were more common among patients taking oseltamivir (8.4%) compared with those taking baloxavir (4.4%) or placebo (3.9%).

In the phase 2 study, the adverse event rate was lower in the three baloxavir dosage groups compared with the placebo group.

The study was supported by Shionogi, which developed baloxavir. Seven authors declared fees from the pharmaceutical industry, including Shionogi. Six authors were employees of Shionogi, one also holding stock. No other conflicts of interest were declared.

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SOURCE: Hayden F et al. N Engl J Med. 2018;379:913-23. doi: 10.1056/NEJMoa1716197.

Live attenuated flu vaccine gets ACIP nod for 2018-2019

BY ANDREW D. BOWSER

MDedge News

The latest seasonal influenza vaccine recommendations from the Advisory Committee on Immunization Practices provide several key updates that will impact clinical practice in the 2018-2019 influenza season.

Of note, live attenuated influenza vaccine (LAIV; FluMist Quadrivalent) is an option, following two seasons in which the committee recommended it not be used.

ACIP also updated its recommendations for individuals with a history of egg allergy, described the vaccine strains chosen for 2018-2019 season, and detailed the changes in age indications for Afluria Quadrivalent and Fluarix Quadrivalent that have been made since publication of its previous guidelines.

Published in MMWR Recommendations and Reports, the updated ACIP recommendations reflect discussions and decisions from the three public meetings of ACIP that have taken place since the last annual update.

All individuals 6 months of age and older who have no contraindications to influenza vaccine should receive routine annual influenza vaccine, ACIP also said in its report, reinforcing a key recommendation that has been in place since 2010.

“To avoid missed opportunities for vaccination, providers should offer vaccination during routine health care visits and hospitalizations,” wrote authors of the report, including lead author Lisa A.

Grohskopf, MD, of the National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta.

Dr. Grohskopf and coauthors made no specific recommendations on which vaccine to use. They said providers should choose licensed, age-appropriate recommended vaccines expected to be available for the 2018-2019 season, including inactivated influenza vaccines (IIV), a recombinant influenza vaccine (RIV4), and the LAIV option.

FluMist Quadrivalent, the one LAIV product expected to be available for the 2018-2019 season, is licensed for individuals aged 2-49 years.

In its deliberations over the updated LAIV recommendation, ACIP reviewed observational data from previous seasons suggesting that the vaccine was poorly effective, and significantly less effective than IIV, against influenza A(H1N1) pdm09 viruses.

The current formulation of FluMist includes a new H1N1pdm09-like vaccine virus. While no effectiveness estimates were available at the time of review, ACIP said it did consider manufacturer data on shedding and immunogenicity for the current vaccine in children between the ages of 24 months through less than 4 years.

“These data suggest that this new H1N1pdm09-like virus has improved replicative fitness over previous H1N1pdm09-like viruses included in LAIV,” Dr. Grohskopf and colleagues wrote.

Individuals with an egg allergy history also can receive any licensed, recommended, age-appropriate IIV, RIV, or LAIV vaccine, said ACIP. This

updated recommendation was based in part on the committee’s review and discussion of three studies that showed no cases of anaphylaxis in egg-allergic children receiving LAIV.

The ACIP recommendation update also outlines the strains selected earlier this year for the 2018-2019 season. Trivalent influenza vaccines in the United States will include an A/Michigan/45/2015 (H1N1) pdm09-like virus, an A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus, and a B/Colorado/06/2017-like virus (Victoria lineage). Quadrivalent vaccines will include those strains plus a B/Phuket/3073/2013-like virus (Yamagata lineage).

The report also acknowledges the recent expansion of age indication for two vaccines that have occurred since the last ACIP recommendations.

Afluria Quadrivalent was previously licensed for individuals 18 years of age and older. In August 2017, the Food and Drug Administration approved expansion of the indication to individuals 5 years of age or older. In January 2018, FDA approved expansion of the Fluarix Quadrivalent indication, previously licensed for age 3 and older, to individuals 6 months and older.

Report coauthor Emmanuel B. Walter disclosed grants from Novavax and Merck. The remaining report authors reported no relevant financial disclosures.

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SOURCE: Grohskopf LA et al. MMWR Recomm Rep. 2018 Aug 24;67(3):1-20.

Pertussis vaccine at birth shows immune response

BY TARA HAELE

MDedge News

Nearly all newborns who received an acellular pertussis-only vaccine at birth showed titers for pertussis and no difference in adverse events, compared with a group receiving only the hepatitis B vaccine, a randomized clinical trial from Australia has found.

“These results indicate that a birth dose of aP vaccine is immunogenic in newborns and significantly narrows the immunity gap between birth and 14 days after receipt of DTaP at 6 or 8 weeks of age, marking the critical period when infants are most vulnerable to severe pertussis infection,” reported Nicholas Wood, PhD, of the National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases in New South Wales, Australia, and his colleagues.

“Administration of the acellular pertussis vaccine at birth has the potential to reduce severe morbidity from *Bordetella pertussis* infection in the first 3 months of life, especially for infants of mothers who have not received a pertussis vaccine during pregnancy,” the researchers concluded in JAMA Pediatrics.

The researchers enrolled 417 infants from Sydney, Melbourne, Adelaide, and Perth between June 2010 and March 2013 and randomized them to receive either the hepatitis B vaccine alone (n = 205) or the hepatitis B vaccine with a monovalent acellular pertussis vaccine (n = 212) within the first 5 days after birth. The randomization was stratified for mothers’ receipt of the Tdap before pregnancy.

The Centers for Disease Control and Prevention currently recommends all newborns receive the hepatitis B vaccine shortly after birth and that pregnant women receive the Tdap vaccine during each pregnancy. There is not currently a monovalent acellular pertussis vaccine licensed in the United States.

The study infants then received the hexavalent



Jacopo Werther/Wikimedia Creative Commons

‘A birth dose of aP vaccine is immunogenic in newborns and significantly narrows the immunity gap between birth and 14 days after receipt of DTaP at 6 or 8 weeks of age, marking the critical period when infants are most vulnerable to severe pertussis infection.’

DTaP-Hib-hep B-polio vaccine and the 10-valent pneumococcal conjugate vaccine at 6 weeks, 4 months, and 6 months.

The primary outcome was detectable levels of IgG antibody to pertussis toxin and pertactin at 10 weeks old.

Of the 206 infants receiving the pertussis vaccine at birth, 93% had detectable antibodies to pertussis toxin and pertactin at 10 weeks, compared with 51% of the 193 infants who received only the hepatitis B shot (*P* less than .001). Geometric mean concentration for pertussis toxin IgG also was four times higher in infants who received the pertussis vaccine at birth.

Adverse events were similar in the two groups both at birth and at 32 weeks, demonstrating that the pertussis birth dose is safe and tolerable.

“More important, in this study, the prevalence of fever after receipt of the birth dose, which can mistakenly be associated with potential sepsis and result in additional investigations in the neonatal period, was similar in both the group that received the aP vaccine at birth and the control group,” the authors reported.

A remaining question is the potential impact of maternal antibodies on protection from pertussis.

“The presence of maternal pertussis antibodies at birth can negatively affect postprimary responses to pertussis, diphtheria, and diphtheria-related CRM197 conjugate vaccines with a variety of infant immunization schedules and vaccines,” the authors noted. “The clinical significance of reductions in pertussis antibody related to maternal interference will require ongoing clinical evaluation, because there are no accepted serologic correlates of protection.”

The research was funded by a Australian National Health and Medical Research Council (NHMRC) grant, and several authors received NHMRC grants. One author also was supported by a Murdoch Children’s Research Institute Career Development Award. GlaxoSmithKline provided the vaccine and conducted the serologic assays. The authors reported having no conflicts of interest.

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SOURCE: Wood N et al. JAMA Pediatr. 2018 Sep 10. doi: 10.1001/jamapediatrics.2018.2349.

Pediatric ED respiratory diagnoses peak in winter

BY RICHARD FRANKI

MDedge News

The two most common reasons for visits to pediatric emergency department exhibit considerable and opposing seasonal variations, according to the Agency for Healthcare Research and Quality.

Of the 30 million ED visits by children aged 18 years and younger during fiscal year 2015, about 9.6 million, or just under 24%, were for respiratory disorders, making it the most common diagnosis by body system. The second-most common reason, injuries, was associated with approximately 7.9 million visits in 2015, the AHRQ reported

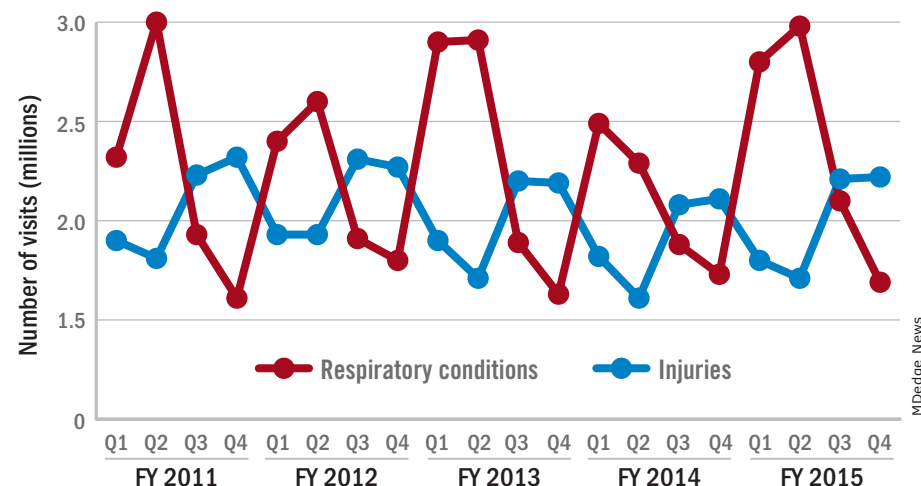
recently in a statistical brief.

Over the 4-year period from 2011 to 2015, pediatric ED visits for respiratory disorders peaked during the months from October to March and dropped during April-September. In 2015, for example, there was a 43% difference between October-December, which was the highest-volume quarter, and July-September, which had the lowest volume of visits, the report showed.

The opposite pattern of seasonality was seen with visits for injury-related visits: The high point each year occurs in April-September, with the low in October-March.

rfranki@mdedge.com

Pediatric ED visits: Seasonal variation in two common diagnoses



Note: Based on data from the Nationwide Emergency Department Sample.

Source: Agency for Healthcare Research and Quality

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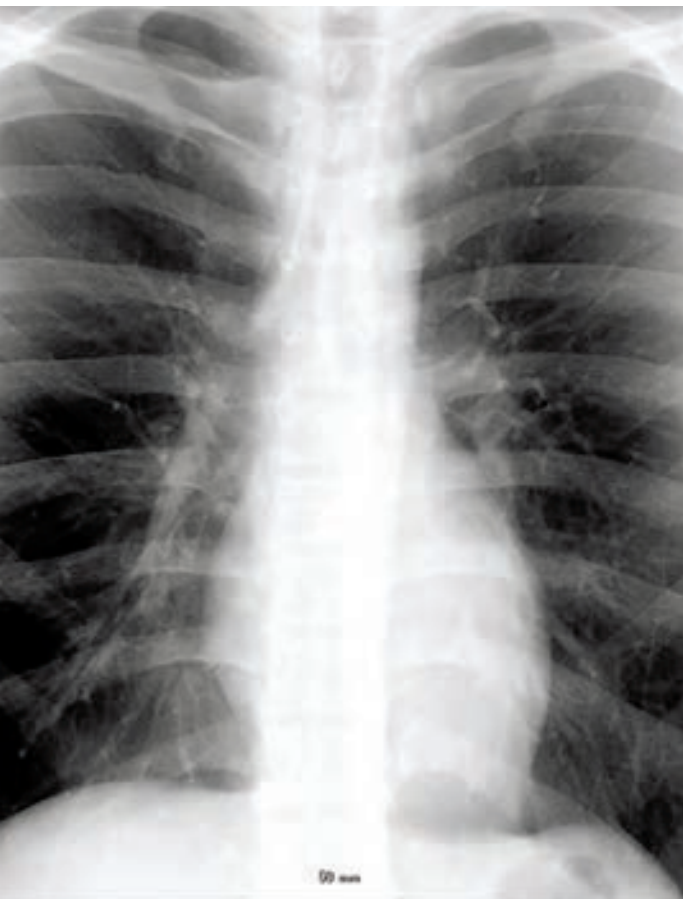
Negative chest x-ray can rule out pediatric pneumonia

BY BIANCA NOGRADY

MDedge News

A negative chest radiograph can be used to rule out the possibility of pneumonia in children suspected of having the disease, and therefore reduce antibiotic use, researchers say.

In a paper published in the September issue of *Pediatrics*, researchers report the results of a prospective cohort study in 683 children – with a median age of 3.1 years – presenting to emergency departments with suspected pneumonia.



Dr. Susan C. Lipsett, from the division of emergency medicine at Boston Children's Hospital, and co-authors, wrote that the use of chest radiograph to diagnose pneumonia is thought to have limitations such as its inability to distinguish between bacteria and viral infection, and the possible absence of radiographic presentations early in the disease in patients with dehydration.

In this study, 457 (72.8%) of the children had negative chest radiographs. Of these, 44 were clinically diagnosed with pneumonia, despite the radiograph results, and prescribed antibiotics. These children were more likely to have rales or respiratory distress and less likely to have wheezing compared with the children with negative radiographs who were not initially diagnosed with pneumonia.

Among the remaining 411 children with negative radiographs – who were not prescribed antibiotics – 5 (1.2%) were subsequently diagnosed with pneumonia within 2 weeks of the radiograph. These five children were all under 3 years of age, but none had been treated with intravenous fluids for dehydration. Only one had radiographic findings of pneumonia on a follow-up visit.

Counting the 44 children diagnosed with pneumonia despite the negative x-ray, chest radiography showed a negative predictive value of 89.2% (95% confidence interval, 85.9%-91.9%). Without those children, the negative predictive value was 98.8% (95% CI, 97%-99.6%).

There were also 113 children (16.5%) with positive chest radiographs, and 72 (10.7%) with equivocal radiographs.

The authors said their results showed that most children with negative chest radiograph would recover fully without needing antibiotics, and argued there was a place for chest radiography in the diagnostic process, to rule out bacterial pneumonia.

“Most clinicians caring for children in the

Susan Millard, MD, FCCP, comments:

I applaud this research and the findings in this article. The number of “recurrent pneumonia” referrals is staggering when the patients never even had one single chest radiograph. Children get multiple antibiotics for “pneumonia,” for example, when they really were having asthma exacerbations and never received a single steroid or even albuterol. A frequent comment in my consultation letter back to the primary is – “further consideration for pneumonia treatment should include confirmation with a chest radiograph.”



outpatient setting rely on clinical signs and symptoms to determine whether to prescribe an antibiotic for the treatment of pneumonia,” they wrote. “However, given recent literature in which the poor reliability and validity of physical examination findings are cited, reliance on physical examination alone may lead to the overdiagnosis of pneumonia.”

They acknowledged that the lack of a universally accepted gold standard for the diagnosis of pneumonia in children was a significant limitation of the research. In addition, the lack of systematic radiographs meant some children who initially had a negative result and recovered without antibiotics may have shown a positive result on a second scan.

No conflicts of interest were declared.

chestphysiciannews@chestnet.org

SOURCE: Lipsett SC et al. *Pediatrics*. 2018;142(3):e20180236.

Alabama ranks first in pediatric asthma prevalence

BY RICHARD FRANKI

MDedge News

The prevalence of pediatric asthma is lowest in Oregon and highest in Alabama, according to estimates from the American Lung Association. The ALA published a report on the prevalence by state of adult and pediatric asthma, chronic obstructive pulmonary disease, and lung cancer. The report can be found at the ALA website (<https://goo.gl/Z1mLdC>).

Oregon's rate comes in at 557 per 10,000 population under the age of 18 years, just ahead of Montana at 574 per 10,000 and Iowa at 577.

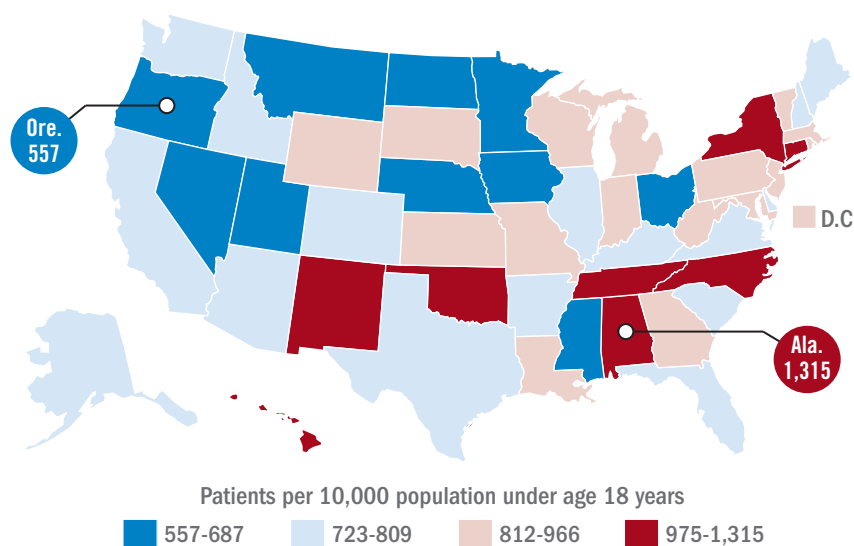
The prevalence of pediatric asthma in Alabama is 1,315 per 10,000, with North Carolina (1,149), Connecticut (1,107), Hawaii (1,026), and New

York (1,005) joining it as members of the over-1,000 club. (MDedge News used the ALA's estimates for persons under age 18 years with asthma in each state and Census Bureau estimates for population to calculate an unadjusted rate for each state.)

The ALA analysis was based on data from the Behavioral Risk Factor Behavioral System surveys for 2016 (31 states), 2015 (District of Columbia, Louisiana, New Hampshire, Texas), 2014 (Alabama, Maryland, North Carolina, Tennessee, West Virginia), 2012 (North Dakota and Wyoming), and 2011 (Iowa). National data were used for eight states (Alaska, Arkansas, Colorado, Delaware, Idaho, South Carolina, South Dakota, Virginia) that had no data available.

rfranki@mdedge.com

Estimated pediatric asthma prevalence



Note: Based on data from the Behavioral Risk Factor Surveillance System.

Source: American Lung Association

Secondhand smoke drives ED visits for teens

BY HEIDI SPLETE

MDedge News

Teens who were exposed to any type of secondhand tobacco smoke were significantly more likely to visit emergency departments and to have more such visits, compared with unexposed controls, based on data from more than 7,000 adolescents. Approximately 35% of U.S. teens spent more than an hour exposed to secondhand smoke in a given week, wrote Ashley L. Merianos, PhD, of the University of Cincinnati and her colleagues.

In a study published in *Pediatrics*, the researchers conducted a secondary analysis of nonsmoking adolescents aged 12-17 years who had not been diagnosed with asthma and who were part of the PATH (Population Assessment of Tobacco and Health) study, a longitudinal cohort trial of tobacco use behavior and related health outcomes in adolescents and adults in the United States. The data were collected between Oct. 3, 2014, and Oct. 30, 2015. The researchers reviewed three main measures of tobacco smoke exposure (TSE): living with a smoker, being exposed to secondhand smoke at home, and being exposed to secondhand smoke for an hour or more in the past 7 days.

Overall, teens who lived with a smoker, had secondary exposure at home, or had at least 1 hour of TSE had significantly more emergency department and/or urgent care visits (mean ranged from 1.62 to 1.65), compared with unexposed peers (mean visits ranged from 1.42 to 1.48). Those who both lived with a smoker and had at least 1 hour of TSE exposure were significantly more likely to visit an ED or urgent care center.

In addition, teens who lived with a smoker, had secondary exposure at home, and had at least 1 hour of TSE were significantly more likely than were unexposed peers to report shortness of breath, difficulty exercising, wheezing during and after exercise, and a dry cough at night (*P* less than .001).

The results were limited by several factors including the use of self-reports of TSE and parent reports of emergency or urgent care visits, and by the inclusion only of other public use variables in the PATH database, the researchers noted. But they adjusted for potentially confounding factors such as household income level, parent education, and health insurance status. "Because adoles-

cents are high users of EDs and/or [urgent care] for primary care reasons, these venues are high-volume settings that should be used to offer interventions to adolescents with TSE and their families," they said.

The researchers had no financial conflicts to disclose. The study was funded by the National Institutes of Health via the National Institute on Drug Abuse and the Eunice Kennedy Shriver National Institute of Child

Health and Human Development.
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SOURCE: Merianos AL et al. *Pediatrics*. 2018 Aug 6. doi: org/10.1542/peds.2018-0266.

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Drainage regimen may promote pleurodesis

BY JEFF CRAVEN

MDedge News

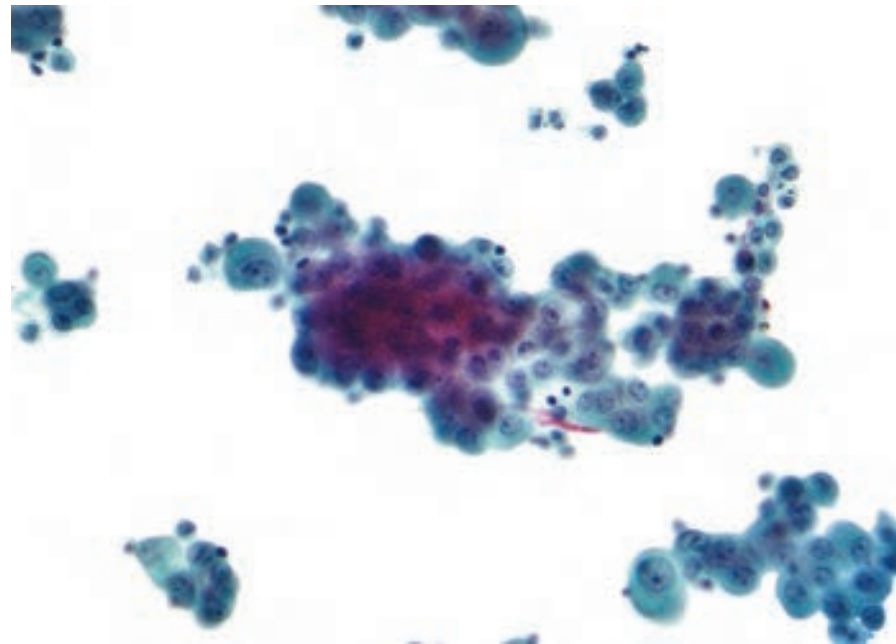
Compared with patients who underwent drainage for treatment of symptomatic malignant pleural effusions that was guided by symptoms, patients who underwent once-daily drainage had similar breathless scores but an increased rate of spontaneous pleurodesis and better quality of life scores, according to recent research published in the *Lancet Respiratory Medicine*.

“In patients in whom pleurodesis is an important goal (e.g., those undertaking strategies involving an indwelling pleural catheter plus pleurodesing agents), aggressive drainage should be done for at least 60 days,” Sanjeevan Muruganandan, FRACP, MBBS, from Sir Charles Gairdner Hospital in Perth, Australia, and his colleagues wrote in their study. “Future studies will need to establish if more aggressive (e.g., twice daily) regimens for the initial phase could further enhance success rates.”

Dr. Muruganandan and his colleagues evaluated 87 patients with symptomatic malignant pleural effusions between July 2015 and January 2017 from 11 centers in Australia, Hong Kong, Malaysia, and New Zealand in the randomized controlled AMPLE-2 trial, in which patients received either once-daily (43 patients) or symptom-guided (44 patients) drainage for 60 days with a 6-month follow-up. Patients were excluded if they had a pleural infection, were pregnant, had a previous pneumonectomy or ipsilateral lobectomy, had “significant loculations likely to preclude effective

fluid drainage,” or had an estimated survival of less than 3 months. Patients were identified and grouped based on whether they had mesothelioma- or nonmesothelioma-type cancer, with cancer type being minimized during randomization.

At 60 days, patients in the aggressive daily drainage group had a mean daily breathless score of 13.1



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mm (geometric means; 95% confidence interval, 9.8-17.4), compared with a mean of 17.3 mm (95% CI, 13.0-22.0) in the symptom-guided drainage group. In the aggressive drainage group, 16 of 43 patients (37.2%) achieved spontaneous pleurodesis at 60 days, compared with 11 of 44 patients (11.4%) in the symptom-guided drainage group ($P = .0049$). At 6 months, 19 of 43 (44.2%) patients in the aggressive drainage group had spontaneous

pleurodesis, compared with 7 of 44 patients (15.9%; $P = .004$) in the symptom-guided drainage group (hazard ratio, 3.287; 95% CI, 1.396-7.740; $P = .0065$).

In each group, the investigators noted adverse events: 11 of 43 (25.6%) patients in the aggressive drainage group and 12 of 44 patients (27.3%) in the symptom-guided

difference in means of 0.112 (95% CI, 0.0198-0.204; $P = .0174$).

The investigators suggested that aggressive drainage may have some unmeasured benefits. “Daily removal of the fluid might have provided benefits in symptoms not captured with our breathlessness and pain measurements. The higher pleurodesis rate, with resultant freedom from fluid (and symptom) recurrence and of the catheter, might have contributed to the better reported quality of life. Additionally, it has been suggested that indwelling pleural catheter drainage gives patients an important sense of control when they are feeling helpless with their advancing cancer.”

They concluded, “For patients whose primary care aim is palliation (e.g., those with very limited life expectancy or significant trapped lung where pleurodesis is unlikely), our data show that symptom-guided drainage offers an effective means of breathlessness control without the inconvenience and costs of daily drainages. The ability to predict the likelihood of pleurodesis will help guide the choice of regimen and should be a topic of future studies.”

Three authors reported serving on the advisory board of CareFusion/BD, two authors reported an educational grant from Rocket Medical (UK), and one author reported an educational grant from CareFusion/BD. The other authors reported no relevant conflicts of interest.

chestphysiciannews@chestnet.org

SOURCE: Muruganandan S et al. *Lancet Respir Med*. 2018 Jul 20. doi: 10.1016/S2213-2600(18)30288-1.

FDA grants full approval to pembrolizumab for NSCLC

BY LAURA NIKOLAIDES

MDedge News

The Food and Drug Administration has now granted full approval to pembrolizumab (Keytruda) in combination with pemetrexed (Alimta) and platinum chemotherapy for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.

The checkpoint inhibitor was previously approved for patients with metastatic nonsquamous NSCLC in 2017, under the accelerated approval process, based on phase 2 results. Approval is now converted to a full approval, based on the results of the phase 3 Keynote-189 trial.

Patients in Keynote-189 who received pem-

brolizumab in combination with pemetrexed and platinum chemotherapy demonstrated a statistically significant and clinically meaningful improvement in overall survival (hazard ratio, 0.49; 95% confidence interval, 0.38-0.64; P less than .00001), according to the company press statement.

There was also a significant improvement in progression-free survival (PFS) with the pembrolizumab plus chemotherapy combination, compared with chemotherapy alone (HR, 0.52; 95% CI, 0.43-0.64; P less than .00001).

Patients with metastatic NSCLC, regardless of programmed death-ligand 1 tumor expression status and with no EGFR or ALK genomic tumor aberrations, were randomized to receive pem-

brolizumab 200 mg, cisplatin or carboplatin, and pemetrexed intravenously every 3 weeks for four cycles followed by pembrolizumab 200 mg for up to 24 months and pemetrexed every 3 weeks ($n = 410$); or cisplatin or carboplatin and pemetrexed intravenously every 3 weeks for four cycles followed by pemetrexed every 3 weeks ($n = 206$). Treatment continued until progression of disease or unacceptable toxicity.

The most common adverse reactions with pembrolizumab, resulting in discontinuation, were pneumonitis (3%) and acute kidney injury (2%). The most common adverse reactions or laboratory abnormalities resulting in interruption of treatment were neutropenia (13%), asthenia/fatigue (7%), anemia (7%), and thrombocytopenia (5%).

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Broad genomic testing of NSCLC in community oncology disappoints

BY SUSAN LONDON

MDedge News

The promise of broad-based genomic sequencing of advanced non-small cell lung cancer (NSCLC) to improve outcomes has not been realized in community oncology, results of a retrospective cohort study reported in JAMA suggest.

Investigators led by Carolyn J. Presley, MD, a thoracic and geriatric medical oncologist at the Ohio State University Comprehensive Cancer Center, Columbus, assessed outcomes among more than 5,500 patients with advanced nonsquamous NSCLC treated mainly in U.S. community practices. Overall, 15% had broad-based genomic testing (next-generation sequencing evaluating more than 30 cancer genes).

Main results showed that, among the patients having broad testing, less than 5% received a targeted treatment based on results that were not attainable with routine testing for common alterations in EGFR and

ALK genes. Moreover, survival after broad testing was not better than that after routine testing.

“This study highlights how broad-based genomic sequencing has disseminated beyond tradi-

tional research settings ahead of a demonstrated association with better survival,” Dr. Presley and her coinvestigators write. They speculate that community uptake is being driven by the ease and cost of ordering a single comprehensive test, perceived benefit, attempts to conserve tissue, and hopes of improved survival if a targeted treatment is available.

“The lack of an association between broad-based genomic sequencing and survival is likely

multifactorial,” the investigators maintain. “First, there were few genetic alterations identified with available targeted treatments. Second, even among those patients for whom targeted treatments were

available, the treatments may not yield a substantial survival benefit or patients may not have had access to targeted agents due to financial barriers. Decision support for clinicians once they receive broad-based genomic sequencing results may also be needed.”

Study details

Dr. Presley and colleagues used the Flatiron Health Database to identify patients with advanced NSCLC who

received care at 191 oncology practices across the United States during 2011-2016. The 5,688 patients studied had stage IIIB, stage IV, or unresectable nonsquamous NSCLC and received at least one line of treatment.

Overall, 15.4% received broad-based genomic sequencing of their tumor, while the rest received routine testing for EGFR and/or ALK alterations only, according to the results reported.

In the broadly tested group, merely 4.5% were given targeted treatment based on testing results. Another 9.8% received routine EGFR/ALK-targeted treatment, and 85.1% did not receive any targeted treatment.

The 12-month unadjusted mortality rate was 49.2% for patients undergoing broad testing, compared with 35.9% for patients undergoing routine testing.

In an instrumental variable analysis done to account for confounding, the 12-month predicted probability of death was 41.1% after broad testing and 44.4% after routine testing ($P = .63$).

Findings were similar in a propensity score-matched survival analysis (42.0% vs. 45.1%; hazard ratio, 0.92; $P = .40$), although there was some suggestion of a benefit of broad testing over routine testing in a Kaplan-Meier analysis among the entire unmatched cohort (HR, 0.69; P less than .001).

“Improved access to research clinical trials in the community setting may improve use of mutational data,” the investigators speculate. “Given the paucity of targeted agents, efforts to increase access to broad-based genomic sequencing should be paired with efforts to facilitate clinical trial enrollment.”

Dr. Presley disclosed that she receives grants from the Yale Lung SPORE Career Development Award, the Robert Wood Johnson/Veterans Affairs Clinical Scholars Program, and The Ohio State University K12 Training Grant for clinical faculty investigators. The study was funded by the Veterans Affairs Robert Wood Johnson Clinical Scholar Program and the Yale Lung SPORE Career Development Award.

chestphysiciannews@chestnet.org

SOURCE: Presley CJ et al. JAMA. 2018 Aug 7. doi: 10.1001/jama.2018.9824.

Among the patients having broad testing, less than 5% received a targeted treatment based on results that were not attainable with routine testing for common alterations in EGFR and ALK genes. Moreover, survival after broad testing was not better than that after routine testing.

VIEW ON THE NEWS

Broad testing may still be warranted

There still may be a role for broad-based genomic testing in patients with NSCLC treated in community oncology practices, according to editorialists Paul A. Bunn Jr., MD, and Dara L. Aisner, MD, PhD. They discussed several study limitations that leave the matter unsettled.

Importantly, the majority of patients in whom this testing identified a potentially treatable alteration did not receive the treatment. “This gap between finding and treating molecular alterations in the community-based clinical setting highlights the reality that obtaining more tumor genomic information must be complemented with clinician education and decision support to understand the importance of matched therapy, and demonstrates a strength of harnessing EMR data to identify potential gaps in practice,” they maintain.

The study did not assess important outcomes other than survival, such as progression-free survival and response rate, Dr. Bunn and Dr. Aisner further note. Previous research has shown that tyrosine kinase inhibitors, for example, improve some of these outcomes without altering survival.

Another limitation was that the study period predated regulatory approval of some relevant targeted therapies and came shortly on the heels of approval of a targeted therapy for ALK rearrangements. And additional therapies are in the

pipeline.

“[T]he incremental value of a cutoff of 30 genes analyzed may place the bar too high to appreciate a survival advantage and the tissue, time, and cost savings due to next-generation sequencing were not considered,” the editorialists point out. The optimal number of genes is unclear and likely to change over time.

Finally, the reports oncologists receive from broad-based genomic sequencing may be long and complex, which may deter them from pursuing appropriate therapy, Dr. Bunn and Dr. Aisner propose.

“The study... provides important insights into how broad-based genomic sequencing is used in the community oncology setting, where the majority of patients with advanced NSCLC in the United States receive care,” they conclude. “However, the limitations of this investigation suggest that the authors’ conclusion that broad testing is not warranted should be tempered to ensure that patients receive the right therapy for the right alteration at the right time.”

Dr. Bunn is with the University of Colorado Cancer Center and department of medical oncology, University of Colorado, Denver and Dr. Aisner is with the University of Colorado Cancer Center and department of pathology, University of Colorado, Aurora. These comments were excerpted from an accompanying editorial.

Score predicts 3-month mortality in malignant pleural effusion

BY BIANCA NOGRADY

MDedge News

A score incorporating clinical and biological markers could help predict the risk of death in patients with malignant pleural effusion and their likelihood of responding well to pleurodesis, according to a study published online in *The Lancet Oncology*.

The researchers used five separate and independent datasets from three

previous multicenter randomized controlled trials – TIME-1, TIME-2, and TIME-3 – to identify 17 candidates for biomarkers of survival at 3 months and 7 candidates for biomarkers of pleurodesis success at 3 months.

They combined these with clinical, radiological, and biological variables to develop the clinical PROMISE model, which included relative protein expression of tissue inhibitor of metalloproteinases 1, platelet-derived growth factor, vascular endothelial growth factor, cadherin 1, and interleukin 4. The pleurodesis dataset included tumor necrosis factor alpha, TNF-beta, interleukin 6, and fibroblast growth factor 2.

The model was then externally validated using complete case data from 162 individuals with malignant pleural effusion, just over one-third of whom had died before 3 months.

The researchers also developed a biological model based on prognostic factors for survival, including use of previous chemotherapy and radiotherapy, baseline ECOG performance status, cancer type, hemoglobin, and white blood cell count.

The researchers found that the PROMISE scores showed “good discrimination,” and based on that, they came up with four categories – A, B, C, and D, representing less than 25% risk, 25%-49% risk, 50%-74% risk, and 75% or more risk of death by 3 months.

“All parameters included in the PROMISE score are independently associated with survival, and thus the identified markers permit some speculation as to their biological role in survival in malignant pleural effusion,” wrote Ioannis Psallidas, MD, of the Oxford Centre for Respiratory Medicine at Oxford (England) University Hospital, and his coauthors.

The study was supported by the Oxford Respiratory Trials Unit, Medical Research Funding-University of Oxford, Slater & Gordon Research Fund, and Oxfordshire Health Services Research Committee Research Grants. No conflicts of interest were declared.

chestphysiciannews@chestnet.org

SOURCE: Psallidas I et al. *Lancet Oncol*. 2018 Jun 13. doi: 10.1016/S1470-2045(18)30294-8.

VIEW ON THE NEWS Need for markers of pleurodesis success remains

Around 50% of patients with a malignancy will present with dyspnea – mostly those with advanced disease. The scientific literature suggests pleurodesis is effective in around 70% of those who undergo the treatment but in real life the proportion can be much lower.

While this study is to be congratulated for introducing a new scoring system to predict survival in malignant pleural effusion, the model did not seem to be able to predict the success of pleurodesis.

The search for predictive markers for successful pleurodesis was one of the most interesting goals of this study, but despite a rigorous analysis of many pleural fluid samples, these markers proved elusive. It may be that identifying even one predictive marker in such a heterogeneous group of primary malignancies is going to be a challenge.

Paul Baas, MD, and Sjaak Burgers, MD, are in the department of thoracic oncology at The Netherlands Cancer Institute in Amsterdam. These comments are taken from their editorial (Lancet Oncol. 2018 Jun 12. doi: 10.1016/S1470-2045[18]30361-9). No conflicts of interest were declared.

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Review protocols to cut device-related HAIs

BY SHARON WORCESTER

MDedge News

ATLANTA – Ongoing vigilance regarding the role of medical devices in health care–associated infections (HAIs) and transmission of antimicrobial-resistant pathogen is needed, according to Isaac Benowitz, MD, of the Centers for Disease Control and Prevention’s Division of Healthcare Quality Promotion (DHQP).

A review of records from the DHQP, which investigates and responds to infections and related adverse events in health care settings upon invitation, showed that in 2017 environmental pathogens were most often the triggers for these investigations, said Dr. Benowitz, a medical epidemiologist.

He reviewed internal records for consultations with state and local health departments involving medical devices and collected data on health care setting, pathogen, investigation findings including possible exposure or transmission, and public health actions.

Of 285 consultations, 48 involved a specific medical device or general medical device reprocessing, he said,

noting that most of those 48 were in an acute care hospital (63%) or clinic (19%).

“The most frequent pathogens noted in these consultations were nontuberculous mycobacteria at 21%, *Candida* species ... at 10%, and *Burkholderia* species ... at 8%,” he said, noting that a wide variety of devices were implicated.

In the inpatient setting these devices included ventilators, dialysis machines, breast pumps, central lines, and respiratory therapy equipment. In the outpatient setting they included glucometers and ophthalmic equipment.

“In many settings we saw issues with endoscopes, including duodenoscopes, but also bronchoscopes,” he added.

Actions taken as part of the investigations included medical device recalls, improved infection control and reprocessing procedures, and patient notification, education, guidance, testing, and treatment.

In some cases there was disciplinary action or oversight for health care professionals, he added.

Investigations identified medical devices contaminated in manu-

facturing, incorrect reprocessing of endoscopes or ventilators, and inappropriate medical device use or reuse, he said.

A number of lessons can be learned from these and other investigations, he added.

“First, devices can be reservoirs and transmission vectors for health care–associated infections. Second, health care facilities, health care facility staff, and public health partners should take opportunities to review protocols and the practices within those protocol,” he said. “These are opportunities to strengthen infection control practices even in the absence of documented transmission.”

In fact, in most of the investigations he discussed, transmission was rarely confirmed to be associated with a medical device. This was largely because of a lack of “epidemiological rigor,” but associations between health care–associated infections and medical devices “are still quite meaningful and often actionable,” he said.

Dr. Benowitz stressed the importance of engaging public health partners to discuss findings and actions, explaining that “what may look like

Eric Gartman, MD, FCCP, comments: This topic is

garnering a significant amount of attention recently given high-profile reports of ineffective cleaning of devices and scopes. It is imperative to strictly follow manufacturers’ protocols for disinfection (as well as any additional local policies), respond to device recalls, and re-train on protocol updates.



a single-facility issue may have a very different perspective when you realize that there’s a similar issue at another facility elsewhere.”

Dr. Benowitz reported having no disclosures.

sworcester@mdedge.com

SOURCE: Benowitz I et al. ICEID 2018, Oral Abstract Presentation E2.

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Guideline offers comprehensive ICU clinical approach

BY WILL PASS

MDedge News

A new ICU clinical practice guideline provides updated strategies for managing adult patients with pain, agitation/sedation, delirium, immobility, and sleep disruption (PADIS).

The guideline builds upon the 2013 Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium (PAD) in Adult Patients in the ICU. Given the comprehensive nature of the PADIS guideline, an accompanying commentary was published simultaneously to help with implementation and interpretation. Both papers are the result of a large-scale, multicenter collaboration and were published in *Critical Care Medicine*.

A panel of 32 international experts, four methodologists, and four survivors of critical illness used the Grading of Recommendations Assessment, Development and Evaluation approach to develop the PADIS guideline.

"Thousands of hours were invested by these guidelines' authors, who were in turn were supported by formal and informal collaborators, over the 3.5 years it took to produce this effort," reported lead author John W. Devlin, PharmD, of the department of pharmacy and health systems sciences, Bouvé College of Health Sciences at Northeastern University, Boston, and his colleagues.

Compared with the 2013 PAD guideline, the PADIS guideline includes new sections regarding rehabilitation/mobility and sleep. "We sought to clarify conceptual definitions within these relatively new critical care research domains," the panel wrote. "The recommendation rationales, fueled by debate and discussion, circled back to the bedside experience – and the perspective of what was best for patients – held by all panelists and methodology experts."

The result is extensive and comprehensive, consisting of both broad and specific descriptions of current ICU practices and associated evidence: The guideline includes 37 recommendations; 32 ungraded, nonactionable statements; and 2 good practice statements. Of note, conditional recommendations far outnumber strong recommendations (34 vs. 3). Reasons for conditional rather than strong recommendations are discussed in rationale sections within the guideline and in the accompanying paper.

"Although our goal was to provide specific recommendations for each question, we suspect some guideline readers may be discouraged by the conditional nature of many recommendations and daunted by the breadth of topics discussed," wrote Michele C. Balas, PhD, of the Ohio State University College of Nursing in Columbus, and her colleagues. Dr. Balas was on the guideline panel and is the lead author of the accompanying article intended to facilitate implementation and interpretation.

One of the more challenging recommendations surrounds the use of antipsychotics for delirious patients. Although this intervention has become relatively common, the guideline stands against it.

"It should be emphasized that there are few supportive data on ICU antipsychotic use and that the initiation of psychoactive medications during critical illness often results in their inappropriate continuation after ICU discharge," wrote Dr. Balas and her coauthors.

Along with a hard look at existing practices, the panel actively sought to expand upon the 2013 guideline with new interventions. Discussions ranged from the less conventional, such as aromatherapy, to the more established, such as polypharmacy. Questions, recommendations, and rationale are clearly described for each topic, with clear supporting evidence. Where evidence



is missing, the panel recommends future research possibilities.

"One example is the consideration of multiple pharmacologic and nonpharmacologic coanalgesic approaches to the ICU patient," wrote Dr. Devlin and his coauthors. "When the published evidence was insufficient, limited to a narrow population or specific intervention (e.g., for procedural analgesia), or outright absent to answer the questions we posed, we structured evidence gap descriptors to inform clinicians where the uncertainty lay, and intended to provide sufficient information to appraise and invite researchers to address these gaps."

The authors disclosed funding from AstraZeneca, Baxter, Covidien, and others.

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SOURCE: Devlin JW et al. *Crit Care Med*. 2018 Sep 1. doi: 10.1097/CCM.0000000000003299; Balas MC et al. *Crit Care Med*. 2018 Sep 1. doi: 10.1097/CCM.0000000000003307.

Hospital setting matters for pneumonia assessment

BY RICHARD FRANKI

MDedge News

Inpatients with pneumonia are just slightly more likely to receive chest x-rays than those in the ED, but there are considerable discrepancies between the two settings for other services, the National Center for Health Statistics (NCHS) reported.

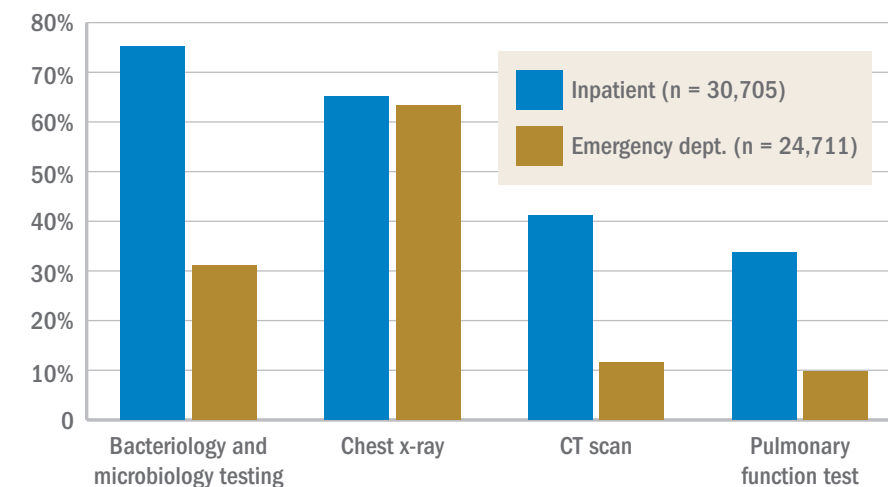
Just over 65% of inpatients with a first-listed diagnosis of pneumonia and 63% of those treated in the ED received a chest x-ray in 2014, according to a National Hospital Care Survey demonstration project involving inpatient claims data from 94 hospitals (30,705 hospitalizations), of which 88 also provided ambulatory claims data (24,711 ED visits).

The percentages were not as close, however, for other diagnostic services. Inpatient stays were much

more likely than ED encounters to involve bacteriology and microbiology testing (75.3% vs. 31.2%), CT

scans (41.2% vs. 11.5%), and pulmonary function tests (33.7% vs. 9.8%), investigators from the NCHS said.

Services received during pneumonia hospitalizations, 2014



Note: Based on data from a National Hospital Care Survey demonstration project.

Source: National Center for Health Statistics

The age distribution of the two patient populations also were quite different, with those aged 65 years and older making up the largest share (46%) of pneumonia inpatients and the 15-and-under group representing the largest proportion (47%) of ED visits. For the inpatient setting, the smallest age group was those aged 15-44 years (10%), and for the ED it was those aged 65 years and older (14%), they reported.

The National Hospital Care Survey "is not yet nationally representative," the NCHS investigators wrote – the overall sample for 2014 consisted of 581 hospitals – but "the number of encounters and the inclusion of [personally identifiable information] allow an example of analysis that was not previously possible."

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Piperacillin-tazobactam fails to outperform meropenem in blood poisoning

BY RANDY DOTINGA

MDedge News

A new study finds that piperacillin-tazobactam doesn't improve mortality compared to meropenem in patients with ceftriaxone-resistant blood poisoning caused by *Escherichia coli* or *Klebsiella pneumoniae*. The findings were so striking that the study was ended early.

"These findings do not support use of piperacillin-tazobactam in this setting," wrote the authors. The report was published Sept. 11 in JAMA (2018;320[10]:984-94.)

According to the Centers for Disease Control and Prevention, an estimated 1,700 deaths in the United States in 2011 were caused by gram-negative bacteria that produce extended-spectrum beta-lactamase enzymes.

While carbapenems such as meropenem

Eric Gartman, MD, FCCP, comments:

The results of this study are very impressive, especially when we recognize that only approximately 7% of these patients were ICU patients and the 30-day mortality of the piperacillin-tazobactam group was 12.3%. Further, there is a suggestion that the dichotomy in results may even be higher in sicker patients and the importance of choice of one antibiotic over another may be further amplified. It is important to note that these patients all had bacteria resistant to ceftriaxone, and narrow-spectrum antibiotics still should be used in more sensitive isolates.

(Merrem) are "regarded as the treatment of choice for serious infections," the MERINO trial (NCT02176122) authors wrote, their rising use could lead to drug resistance.

One alternative option is to embrace beta-lactam/beta-lactamase inhibitors such as piperacillin-tazobactam (Zosyn), the researchers noted, but research has produced conflicting results.

Piperacillin-tazobactam is an injected penicillin antibiotic used to treat conditions such as severe pneumonia, complicated urinary tract infections and complicated skin and soft-tissue infections.

For the new study, researchers led by Patrick N.A. Harris, MBBS, of the University of Queensland, randomly assigned 188 patients to intravenous piperacillin-tazobactam (4.5 g every 6 hours) and 191 patients to meropenem (1 g every 8 hours) for 4-14 days, depending on clinician's preference (12 other patients did not continue with the study after initial randomization because of factors such as errors).

All patients were adults and had at least one blood test showing they were positive for *E. coli* or *K. pneumoniae*. They all had to be nonsusceptible to ceftriaxone (Rocephin) but susceptible to piperacillin-tazobactam.

The study was ceased prior to enrollment because of the risk of harm. Interim findings suggested the study was unlikely to show higher effectiveness for piperacillin-tazobactam

The primary analysis included 379 patients (mean age 67 years, 48% were women), and the primary outcome analysis included 378 patients.

A total of 23 (12.3%) of 187 patients in the piperacillin-tazobactam group died by 30 days compared to 7 (3.7%) of 191 in the meropenem group (risk difference, 8.6%; $P = .90$ for noninferiority).

By day 4, 68% of the piperacillin-tazobactam group and 75% of the meropenem group achieved clinical and microbiological resolution.

Serious adverse effects other than death were rare, occurring in around 3% of the piperacillin-tazobactam group and nearly 2% of the meropenem group.

The researchers note various limitations, including the unblinded nature of the study and the fact that it's not known if extended or continuous infusions of piperacillin-tazobactam would boost the drug's effectiveness. They also note that delays resulted in some patients initially receiving treatment with one of the study's two drugs before being randomized to the other.

The study authors caution that it's not clear if newer beta-lactam/beta-lactamase inhibitors agents such as ceftolozane-tazobactam or ceftazidime-avibactam may be effective in this population.

The study was funded by the University of Queensland, Australian Society for Antimicrobials, International Society for Chemotherapy, and National University Hospital Singapore. Various organizations funded the researchers and the study's whole-genome sequencing. The study authors report various disclosures, including funding from drugmakers such as Pfizer, maker of Zosyn (through its subsidiary Wyeth) and Merrem.

Commentary coauthor Mary K. Hayden reports research funding from Colorox and serving as an investigator on research products that received product support from Sage Corporation, Molnlycke, Clorox, OpGen, and Medline.

chestphysiciannews@chestnet.org

SOURCE: Harris PNA et al. JAMA. 2018 Sep 11;320[10]:984-94. doi: 10.1001/jama.2018.12163.

Cost led to missed care for 4.5% of Americans in 2017

BY RICHARD FRANKI

MDedge News

The percentage of Americans who went without medical care because of cost rose to 4.5% in 2017, reversing a 6-year trend, the National Center for Health Statistics reported.

The rate was 4.4% in 2016, which represented a slowdown in what had been steady decline over the previous 5 years, according to data from the National Health Interview Survey. Declining rates corresponded with the implementation of early provisions of the Affordable Care Act in 2010.

The 2017 rate varied considerably by age group. Not surprisingly, more working-age people – those aged 18-64 years – reported that they did

not seek medical care at some point in the previous 12 months because of cost (6.1%). The rate was 1.2% for those under 18 years and 2.7% for

the Medicare eligible – those aged 65 years and older.

For 2016, the rates were 6.2% for those aged 18-64 years, 1.2% for the under-18 group, and 2.1% for the 65+ group, the data show.

Among females of all ages in 2017, 4.8% failed to get needed care at some point in the previous year, compared with 4.1% of men. Those numbers were unchanged from 2016 but down from 4.9% for females in 2015 and up from 4.0% for males that year, the NCHS said.

In 2017, the rate also varied by race/ethnicity – 4.1% for whites, 5.3% for Hispanics, 6.1% for blacks – and by location – 4.1% for large metropolitan areas, 4.9% for small metro areas, and 5.5% for rural locales, according to the early release of survey data.

rfranki@mdedge.com

Persons who failed to obtain needed medical care because of cost



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

Source: National Center for Health Statistics

Brain connectivity in depression linked to sleep quality

BY NICOLA GARRETT

MDedge News

An increase in functional connectivity in certain regions of the brains of people with depression could explain the link between the disease and poor sleep quality – and could have implications for the treatment of both conditions, the first research of its kind suggests.

Wei Cheng, PhD, of the Institute of Science and Technology for Brain-Inspired Intelligence at the Fudan University in Shanghai, China, and colleagues noted that many people with depression report poor sleep quality and sleep disturbance.

“Understanding the neural connectivity that underlies both conditions and mediates the association between them is likely to lead to better-directed treatments for depression and associated sleep problems,” they wrote in *JAMA Psychiatry*.

In the current study, the research team used data from 1,017 participants of the Human Connectome Project drawn from the general population in the United States (who were not selected for symptoms of depression). Subjects, whose ages ranged from 22 to 35 years, had

completed the Adult Self-Report of Depressive Problems portion of the Achenbach Adult Self-Report for Ages 18-59 – a survey of self-reported sleep quality and resting-state functional MRI. “The sleep phenotype of participants in the HCP was assessed by the self-reported PSQI total score, which combines seven component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction in the past month.”

The investigators noted, that “resting-state functional connectivity between brain areas, which reflects correlations of activity, is a fundamental tool in augmenting understanding of the brain regions with altered connectivity and function in mental disorders.”

The researchers then cross-validated the sleep findings using a sample of 8,718 participants from with the United Kingdom Biobank data set.

In total, the research team identified 162 functional connectivity links involving areas associated with sleep, with 39 of these areas also associated with Depressive Problems Scores (*P* less than .001).

Overall, the brain areas with increased functional connectivity associated with the Pittsburgh Sleep Quality Index score and Depressive Problems scores included the lateral orbitofrontal cortex, dorsolateral prefrontal cortex, anterior and posterior cingulate cortices, insula, parahippocampal gyrus, hippocampus, amygdala, temporal cortex, and precuneus.

A mediation analysis conducted by the authors aimed at assessing the underlying mechanisms showed that “these functional connectivities underlie the association of depressive problems score with poor sleep quality (*P* less than .001).”

They observed “much smaller” associations in the reverse direction – in that the associations of sleep quality with depressive problems mediated by these links were less significant.

“These findings provide a neural basis for understanding how depression is associated with poor sleep quality, and this in turn has implications for treatment because of the brain areas identified,” the research team concluded.

Dr. Cheng and colleagues cited several limitations. One is that the Depressive Problems scores used

were not reflective of a formal diagnosis. Nevertheless, they said, the current findings provided “strong support” for the role of the lateral orbitofrontal cortex in depression, particularly as the investigators observed relatively high correlations with functional connectivities in this area of the brains of 92 participants who had been diagnosed with a major depressive episode over their lifetime.

“The understanding that we developed in this study is consistent with areas of the brain involved in short-term memory (the dorsolateral prefrontal cortex), the self (precuneus), and negative emotion (the lateral orbitofrontal cortex) being highly connected in depression which results in increased ruminating thoughts that are at least part of the mechanism that impairs sleep quality,” they added.

The study was supported by several entities, including the Shanghai Science & Technology Innovation Plan and the National Natural Science Foundation of China. No conflicts of interest were reported.

chestphysiciannews@chestnet.org

SOURCE: Cheng W et al. *JAMA Psychiatry*. 2018 Jul 25. doi: 10.1001/jama-psychiatry.2018.1941.

App tied to reducing insomnia, depression in adults

BY KERRY DOOLEY YOUNG

MDedge News

ROCKVILLE, MD. – Using a digital application could allow more adults to try cognitive-behavioral therapy (CBT) to combat insomnia and expand access to a technique that’s been shown to ward off depression, a researcher said at a National Institute of Mental Health conference on mental health services research.

Previous research has shown that CBT for insomnia (CBT-I) that’s conducted in person is not only effective for insomnia but also can reduce co-occurring depression. In fact, the treatment effects for depression are roughly the same magnitude as antidepressants but with fewer side effects and contraindications, said Philip C. Cheng, PhD, of the Sleep Disorders & Research Center at the Henry Ford Health System in Detroit. He cited a systematic literature review published recently that found CBT-I to be a promising treatment for depression comorbid with insomnia (*J Psychosom Res*. 2018 Mar;106:1-2).

“We’ve got a two-birds-with-one-stone kind of a deal,” Dr. Cheng said, referring to the ability of CBT-I to address both disorders. “It’s hard to resist the impulse to say: ‘This is great. Let’s get this out to everyone who has insomnia.’”

But there’s only a limited pool of about 1,200

health care professionals experienced in CBT-I to serve a much larger pool of people who might need help warding off depression, he said. The NIMH estimates that 16.2 million adults in the



DR. PHILIP C. CHENG

United States had at least one major depressive episode in 2016, which is about 6.7% of all U.S. adults. To address the shortage, developers have created digital apps such as Sleepio, which Dr. Cheng and his colleagues used in their research.

For this study, they recruited people with insomnia who did not at the time have depression. Patients were assigned to

either use the Sleepio app or follow a more traditional sleep education program. The latter consisted of six weekly emails with tips on sleep hygiene, Dr. Cheng said. These contained the typical messages that a patient would receive from a physician to address a sleep disorder, he added.

“The doctor says: ‘Don’t drink caffeine; make sure you sleep in a dark room,’ things like that,” Dr. Cheng said. “A lot of evidence has shown that this is not an effective stand-alone treatment for insomnia.”

With Sleepio, users get online assistance in ad-

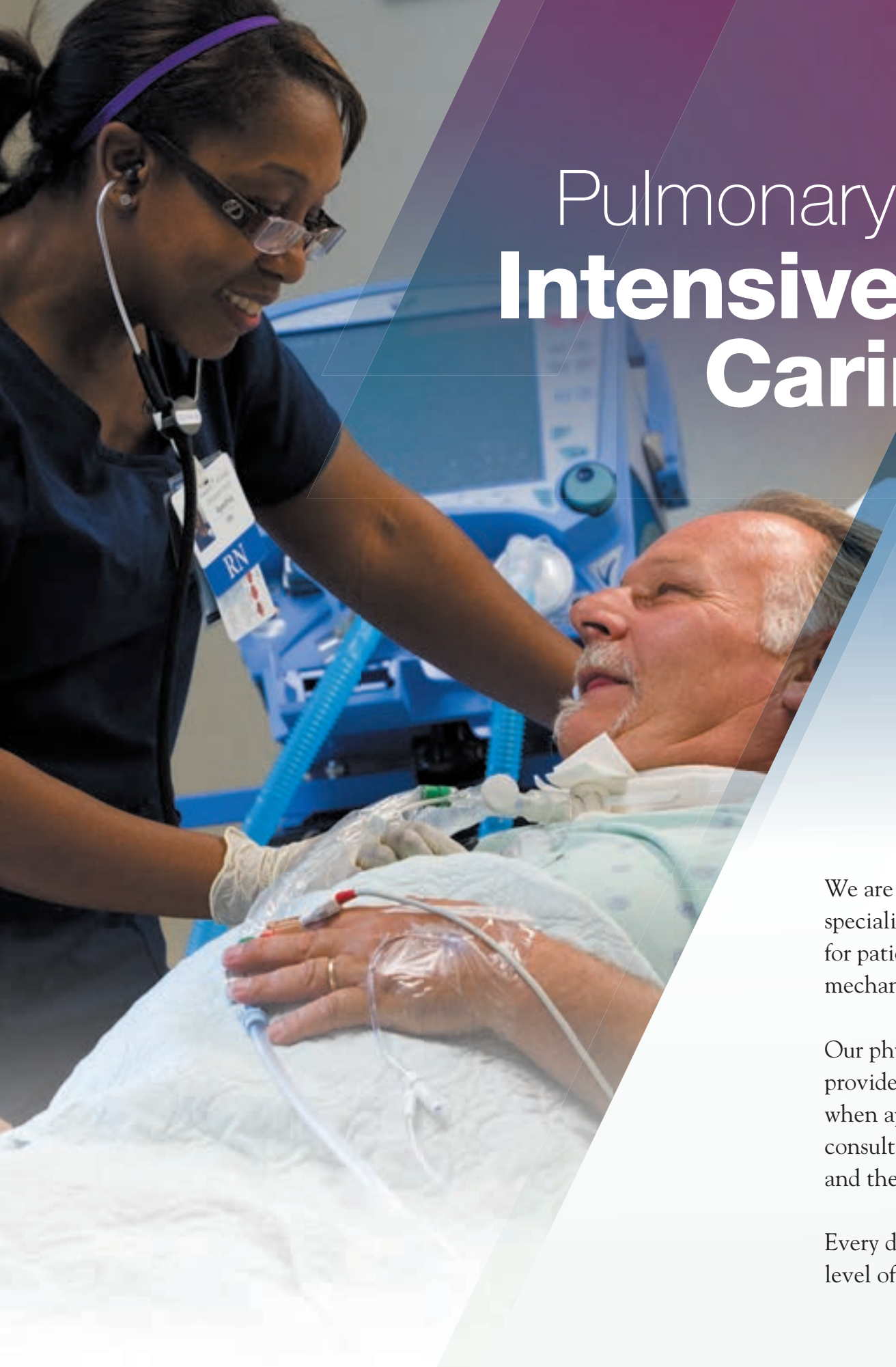
ressing their challenges with sleep. Dr. Cheng said he and his colleagues used Sleepio because of its grounding in CBT methods. Other apps built with the same commitment to CBT might deliver similar results, according to Dr. Cheng. He presented the results seen in 166 people who used the digital CBT-I approach and 146 who received sleep education.

An interim analysis of results showed that, within a period of 12 months after treatment, 20% of those in the sleep education control group developed incident depression, whereas only 10% of those in the CBT-I did, Dr. Cheng said. Analyzing the results, Dr. Cheng and his colleagues said those numbers indicate that the number needed to treat to prevent one case of depression was 10.

The subscription for this online tool costs about \$400 a year, so it would cost \$4,000 to prevent one case of depression, Dr. Cheng said.

The Robert Wood Johnson Foundation funded the study. Dr. Cheng also is funded by a National Institutes of Health grant (K23HL138166). Sleepio provided its product for the study free of charge. Dr. Cheng said that he has no relevant conflicts of interest and that he has funding from Harmony Biosciences for a study unrelated to this work.

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Opioid use impacts sleep in chronic pain patients

BY HEIDI SPLETE

MDedge News

Patients with chronic pain who took opioids reported significantly more difficulty falling asleep, compared with those who didn't use opioids, a study of 144 adults has found.

"Identification of factors that influence insomnia symptoms among adults with chronic pain may inform prevention and treatment efforts for both disorders," wrote Mary Beth Miller, PhD, of the University of Missouri School of Medicine, Columbia, and her colleagues.

To identify the potential impact of opioid use on sleep among chronic pain patients, the researchers recruited adults reporting symptoms of both insomnia and fibromyalgia. The average age of the participants was 52 years, and 95% were women. The study findings were published in *Sleep Medicine*.

The participants completed sleep diaries for 14 days, during which they recorded data including when they went to bed, how long it took them to fall asleep (SOL), how often they woke up during the night

and how long they stayed awake (WASO), what time they woke up, and what time they got out of bed. Patients also reported "yes" or "no" on opioid use and their dosage each day and rated their pain on a scale of 0-100 each night before retiring.

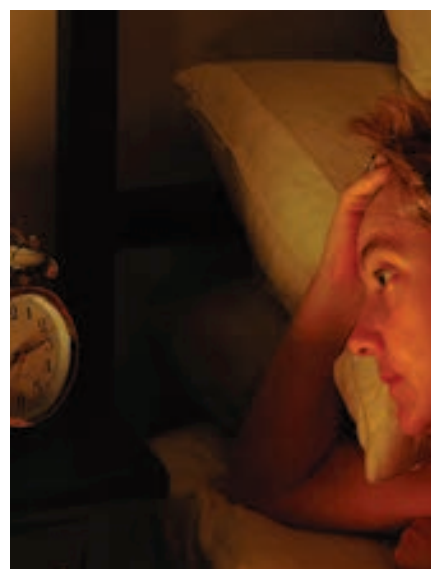
The study participants wore wrist actigraphy devices for baseline assessment and underwent 1 night of ambulatory polysomnography.

The researchers used a multiple regression model to examine how pain intensity affected the association between opioid use and insomnia.

Overall, "opioid use was not associated with improvements in insomnia symptoms across any level of pain intensity, and was associated with worse insomnia symptoms among those reporting less intense pain," the researchers said.

Opioid use was associated with significantly longer time to sleep onset in participants with low levels of pain ($P = .02$) but not among those with moderate to high levels; average sleep onset latency appeared unaffected by pain level among participants who did not use opioids.

The study findings were limited by several factors including the



Karen Winton/Stockphoto

cross-sectional nature of the analysis, the researchers noted. However, from a clinical perspective, the "findings suggest that it may be important to advise patients reporting symptoms of insomnia about the risks of extending time in bed when providing them with opioid pain medication and that the use of behavioral or cognitive-behavioral treatment for insomnia may be recommended," they said. The researchers also recommended that future studies address the longitudinal associations between opioid use and insomnia.

The researchers had no financial conflicts to disclose.

chestphysiciannews@chestnet.org

small number of male participants, the use of paper forms for the sleep diaries, which prevented confirmation of timely reporting, and the

SOURCE: Miller MB et al. *Sleep Med.* 2018. doi: 10.1016/j.sleep.2018.08.015.

Obstructive sleep apnea linked to gout

BY HEIDI SPLETE

MDedge News

Adults with obstructive sleep apnea are approximately twice as likely as are those without it to develop gout, according to data from a large, retrospective study with a median 5-year follow-up.

Data from previous studies have shown an increased risk in developing gout within the first year of an obstructive sleep apnea (OSA) diagnosis, wrote Milica Blagojevic-Bucknall, PhD, of Keele (England) University, and her colleagues. Research on the link between OSA and gout has suggested a common mechanism in these two conditions (*J Clin Sleep Med.* 2018 Aug 30 [Epub ahead of print]; *Arthritis Rheumatol.* 2015 Dec;67[12]:3298-302).

In a study published in *Arthritis & Rheumatology*, the researchers compared 15,879 patients with OSA and 63,296 without.

Overall, 4.9% of OSA patients and 2.6% non-OSA controls developed gout over a median follow-up period of 5.8 years. The incidence rate for gout per 1,000 person-years was 7.83 among patients with OSA and 4.03 for controls (adjusted hazard ratio, 1.42). The greatest risk for gout in the OSA patients occurred approximately 1-2 years after their diagnosis.

The researchers also found signifi-

cant associations between body mass index and gout risk in sleep apnea across all BMI categories, but the strongest association occurred in the normal BMI group (HR, 2.02) at 2-5 years after the index date of OSA.

"The novelty of this study lies in assessing both the short- and long-term association of OSA with incident gout in a large primary care-based population," the researchers said. They proposed that the most likely explanation for the events was that "intermittent hypoxia increases nucleotide turnover which enhances endogenous uric acid production."

The study findings were limited by several factors including potential misclassification of OSA and the impact of confounding variables such as genetics and diet, they noted.

However, the results support the association between sleep apnea and gout, but also serve to highlight that clinicians should "consider the possibility of gout in patients with sleep apnea regardless of obesity," the researchers wrote.

The National Institute for Health Research funded the study. The authors have no conflicts of interest to declare.

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SOURCE: Blagojevic-Bucknall M et al. *Arthritis Rheumatol.* 2018 Aug 30. doi: 10.1002/art.40662.

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Expert panel updates guidelines on antithrombotic therapy for atrial fibrillation

BY ANDREW D. BOWSER

MDedge News

FROM THE JOURNAL CHEST® ■ For patients with atrial fibrillation with at least one risk factor besides gender, oral anticoagulation is the optimal choice of antithrombotic therapy, experts said in a comprehensive, updated guideline.

The 113-page guideline, published in the journal *CHEST*®, provides antithrombotic treatment recommendations for atrial fibrillation based on different levels of risk for stroke and in a variety of clinical presentations.

Altogether, the new guidelines highlight 60 key recommendations from the 12-person expert panel, chaired by Gregory Y.H. Lip, MD, of the Institute of Cardiovascular Sciences, University of Birmingham (England).

To develop the guidelines, the panel conducted a systematic literature review of relevant articles released since the 2012 publication of *Thrombotic Therapy: American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines (9th Edition)*.

Since that time, “there have been substantial developments in atrial fibrillation thromboprophylaxis, whether with regard to risk assessment, antithrombotic drugs, or non-drug approaches,” panelists said in their report.

The panel graded the quality of the new evi-

dence found in the literature review, and then undertook a consensus development process. Each recommendation and statement required at least 80% consensus to pass.

Their treatment recommendations in the report are focused on three topic areas: stroke and bleeding risk assessment, antithrombotic therapy in general, and antithrombotic therapy in special situations, such as acute coronary syndrome and stenting, chronic atrial flutter, pregnancy, and chronic kidney disease.

Stroke prevention is the main priority in a “holistic approach” to management of atrial fibrillation, the panelists said in the report.

“Many of the risk factors leading to incident AF are also risk factors for ischemic stroke, and the promotion of an integrated or holistic approach to AF management is needed, incorporating stroke prevention, addressing symptoms and risk factor management,” they said.

No antithrombotic therapy is needed for patients who have atrial fibrillation without valvular heart disease, the panelists concluded.

For patients with at least one nongender CHA₂DS₂-VASc stroke risk factor, oral anticoagulation is recommended over aspirin, aspirin and clopidogrel, or no therapy, they said.

In high-risk patients, including males with two or more CHA₂DS₂-VASc risk factors and females with three or more, novel oral anticoagulants are

recommended over adjusted-dose warfarin, they added.

At each patient contact, patients with atrial fibrillation should receive bleeding risk assessment starting with potentially modifiable risk factors such as uncontrolled blood pressure or excessive alcohol intake, according to the expert panel.

High-risk patients, as indicated by a HAS-BLED score of 3 or greater, should have more frequent and regular follow-up, they said.

The expert panel report concludes with a discussion on practical and patient-centered issues.

“Patient education is essential to provide patients with sufficient information to enable them to make an informed decision about whether or not they wish to take oral anticoagulants, and if they do, which oral anticoagulant they would prefer,” Dr. Lip and his colleagues said in their report.

Dr. Lip disclosed a potential conflict of interest with Boehringer Ingelheim. Expert panel members reported disclosures related to Boston Scientific, Medtronic, St. Jude Medical, Biotronik, MSD, Novartis, Pfizer, Bayer, Servier, Gilead, Bristol-Myers Squibb, AstraZeneca, and others.

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SOURCE: Lip GYH et al. *CHEST*. 2018 Aug 21. pii: S0012-3692(18)32244-X.

Algorithm targets circulation time to predict CV risk

BY RICHARD MARK KIRKNER

MDedge News

BALTIMORE – Researchers have developed an algorithm to calculate circulation time during sleep that may provide another tool to identify the risk of underlying cardiac vascular disease in patients with sleep apnea, one of the study’s lead investigators reported at the annual meeting of the Associated Professional Sleep Societies.

“There’s always been a question that there could be some global or untapped physiological indices that might give us some glimpse into future cardiovascular events or instantaneous cardiovascular vulnerability during sleep apnea events,” said Younghoon Kwon, MD, assistant professor of cardiovascular medicine at the University of Virginia, Charlottesville. “Circulation time that can be derived from a sleep study may be one of these novel indices. Although it has been examined in patients with heart failure with Cheyne-Stokes respiration, it has rarely been studied in patients

with obstructive sleep apnea without heart failure.”

He noted that in this study, which utilized a cohort of 686 patients from the Multi-Ethnic Study of



DR. KWON

Atherosclerosis (MESA), all with an apnea-hypopnea index greater than 15, the automated algorithm the researchers developed to calculate lung-to-finger circulation was correlated highly

with visual measurement. The algorithm used randomly selected polysomnograms from the MESA cohort. It employed the airflow/nasal signal and the oxygen saturation signal, using the visually scored start and endpoint of apnea/hypopnea as a starting point. For each event, the calculation identified two key points: the endpoint of apnea/hypopnea and the endpoint of desaturation to arrive at a calculation of lung-to-finger circulation,

Dr. Kwon explained.

The significance of the findings was the correlation between the visual and automated methods of calculating lung-to-finger circulation time. In a matched subgroup of 25 subjects, the correlation was around 95% (*P* less than .0001); in all cases, the correlation was around 69% (*P* less than .001). In matched cases, the average lung-to-finger circulation times were identical with visual and automated techniques: 19.5 seconds (*P* = .92), whereas in all cases the averages differed: 19.6 seconds for visual versus 18.6 seconds for automated (*P* = .42).

“The results showed that the visual against the automated circulatory time measurement was very good,” Dr. Kwon said.

With this algorithm, multiple circulation time measures were automatically derived for each sleep study. Subsequently, average circulation time was derived for each study participant. The average circulation time was 19.4 seconds in the entire cohort, versus 21.0 seconds in those with apnea and 17.6 seconds in patients with hypopnea.

“Older age, male gender, and higher obstructive sleep apnea severity appeared to be independently associated with higher than average lung-to-finger circulation times,” Dr. Kwon said. “However, there was no apparent association between the obstructive event length or the severity of oxygen desaturation and the respective circulation time within subjects. Similarly, sleep positions and sleep stages do not seem to bear any association.”

One of the limitations of the study, he noted, was its assumption of the automated algorithm as the threshold and somewhat limited candidate variables. Future studies should involve more diverse cohorts with prevalent cardiovascular disease to determine the utility of the algorithm in predicting cardiovascular events, he said.

Dr. Kwon reported having no financial relationships, and the American Academy of Sleep Medicine Foundation provided study funding.

chestphysiciannews@chestnet.org

SOURCE: Kwon Y et al. *SLEEP* 2018, Abstract #0450.

Short sleep may mean elevated blood pressure

BY M. ALEXANDER OTTO

MDedge News

CHICAGO – Consider 24-hour ambulatory blood pressure monitoring when patients complain about not getting enough sleep. You might catch hypertension early, according to researchers from the University of Pennsylvania, Philadelphia, and elsewhere.

They found a strong association between elevated 24-hour systolic blood pressure and short sleep duration, less than 7 hours a night and a mean in the study of 5.5 hours. Every 2-2.5 minutes of lost sleep was associated with an increase of 1 mm Hg in 24-hour mean systolic blood pressure and a increase of 1 beat per minute in heart rate.

The relationship was independent of office BP, nocturnal dipping status, and BP variability. It held in both the obese and nonobese, and in patients with and without obstructive sleep apnea (OSA).

“Adults with shorter sleep duration may benefit from screening with 24-hour ambulatory BP monitoring to promote earlier detection of hypertension and potentially mitigate the” the risk of cardiovascular disease. “This may be particularly important in screening for masked hypertension,” meaning normal pressures in the office, but elevated pressures at home, said investigators led by Jordana Cohen, MD, of the department of medicine at the University of Pennsylvania in a presentation at the joint scientific sessions of AHA Council on Hypertension, AHA Council on Kidney in Cardiovascular Disease, and American Society of Hypertension.



DR. COHEN

Dr. Cohen suggested that perhaps the sympathetic and endothelial derangements that drive hypertension in OSA also affect people with insufficient sleep. It may be that the normal morning surge in blood pressure persists longer into the day, she suggested. The investigative team analyzed data from two studies. The first, LIMBS (Lifestyle Modification in BP Lowering Study), was a phase 2 trial assessing yoga for blood pressure lowering. The new analysis included 66 LIMBS subjects who had 24-hour blood pressure monitoring and kept sleep diaries

to record their sleep duration (J Clin Hypertens [Greenwich]. 2016 Aug;18[8]:809-16).

The team also analyzed 153 subjects from the PISA (Penn Icelandic Sleep Apnea) cohort, an ongoing project assessing continuous positive airway pressure for OSA, among other things. PISA includes patients with OSA, diabetes, hypertension, and kidney or cardiovascular disease. Sleep duration in the 153 subjects was again self-reported, but corroborated by actigraphy (J Sleep Res. 2015 Jun;24[3]:328-38).

The new findings were driven mostly by higher daytime systolic BP among short sleepers in LIMBS, and higher systolic pressures during both day and night among short sleepers in PISA, compared with subjects who slept at least 7 hours, and a mean of 8.5 hours.

In LIMBS, the mean 24-hour systolic BP was 12.7 mm Hg higher and the average heart rate 8 bpm faster among short sleepers; in PISA, the mean 24-hour systolic BP was 4.7 mm Hg higher and the heart rate 2 bpm faster.

The work was funded by the National Institutes of Health. The investigators had no disclosures.

aotto@mdedge.com

High-sensitivity cardiac troponin levels associated with poor cardiovascular outcomes in COPD patients

BY ANDREW D. BOWSER

MDedge News

In patients with chronic obstructive pulmonary disease (COPD) and heightened cardiovascular risk, high levels of high-sensitivity cardiac troponin are strongly associated with risk of poor cardiovascular outcomes, according to a post hoc analysis of a clinical trial.

An increased risk of cardiovascular adverse events and cardiovascular death was seen in COPD patients in the highest quintile of plasma cardiac troponin concentrations at baseline, results of the analysis show.

The findings highlight the potential utility of high-sensitivity cardiac troponin in both clinical trials and clinical practice, according to researcher Nicholas L. Mills, MD, The University of Edinburgh, and coinvestigators.

“Recognizing the risk associated with increased troponin concentrations might encourage clinicians to address cardiovascular risk due to lifestyle choices, and make patients more likely to engage with these recommendations,” Dr. Mills and co-authors wrote in the Journal of the American College of Cardiology.

The analysis by Dr. Mills and colleagues was based on assessment of cardiac troponin I concentrations for patients in SUMMIT, a

randomized trial assessing inhaled corticosteroids and long-acting beta-agonists in COPD patients with elevated cardiovascular risk.

Compared with those in the lowest quintile, patients in the highest quintile of baseline plasma cardiac troponin concentrations had an increased risk of a cardiovascular composite event, even after adjusting for

confounding variables (hazard ratio, 3.67; 95% confidence interval, 1.33-10.13; $P = .012$). Increased risk of cardiovascular death was also seen in the highest quintile as compared with the lowest quintile (HR, 20.06; 95% CI, 2.44-165.15; $P = .005$).

The research was supported by GlaxoSmithKline and a Butler British Heart Foundation Senior Clinical Research Fellowship received by Dr. Mills. Disclosures reported by Dr. Mills and coauthors included consultancy, research grants, and speaker fees from a variety of commercial sources.

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SOURCE: Adamson PD et al. J Am Coll Cardiol. 2018 Sep 4;72(10):1126-37.

VIEW ON THE NEWS

‘Robust’ findings have implications for clinical practice

The current study data are “robust” and suggest a strong association between high-sensitivity cardiac troponin values and cardiovascular event risk in these COPD patients, according to authors of an editorial.

The study also showed that a change in high-sensitivity cardiac troponin at 3 months is associated with increased risk, noted editorial authors Allan S. Jaffe, MD, and H. Ari Jaffe, MD.

“Most of these events probably represent acceleration of atherosclerosis, given the effects of smoking on atherosclerotic disease and its progression,” the authors said in the Journal of the American College of Cardiology.

However, study authors could have more extensively addressed how to use that information to improve the care of COPD patients at elevated cardiovascular event risk, they added.

A “pilot algorithm” that could be used to apply this biomarker analysis in clinical practice was

proposed in an editorial accompanying the research report.

They suggest repeating high-sensitivity cardiac troponin measurements to reduce variability, as well as repeating samples at 3 months to detect changes that could signal increased risk.

“In addition, one should avoid decisions based on small differences,” they wrote.

Dr. Allan S. Jaffe is with the department of cardiovascular medicine and the department of laboratory medicine and pathology at the Mayo Clinic in Rochester, Minn. He reported serving as a consultant for Beckman, Abbott, Siemens, ET Healthcare, Sphingotec, Becton Dickinson, Quindel, and Novartis. Dr. H. Ari Jaffe is with the department of medicine, pulmonary division at University of Illinois at Chicago, Jesse Brown VA Medicine Center, Chicago. He reported he has no relationships to disclose relevant to the contents of the editorial.

Welcome, Dr. Cowl!

As we greet our new CHEST President, Clayton T. Cowl, MD, MS, FCCP, we asked him for a few thoughts about his upcoming presidential year. He kindly offered these responses:

What would be one of the many things you would like to accomplish as President of CHEST?

We plan to increase the engagement of our membership, and, in doing so, allow for more opportunities to serve in leadership roles, educate as faculty, or to participate in more of the wide array of educational opportunities within CHEST – whether the member is a long-tenured physician, a trainee, an earlier career researcher or educator, or a colleague in the care team, such as a respiratory therapist, advanced practice provider, or a pharmacist.

CHEST has been and will continue to be a leader in delivery of education and will further advance opportunities to present breaking research. Ultimately, the reason we are in medicine is to improve the care that we deliver to our patients, so it is incumbent upon us to keep the mission aimed toward “patient-centric” goals.

What do you consider to be the greatest strength of CHEST, and how will you build upon this during your Presidency?

Our greatest strength is our members, who bring a diversity of experience, expertise, and passion for what they do at the forefront. Together, with our incredibly talented and dedicated support staff at CHEST, as well as our industry and publishing partners, our organization is poised to bring medical education in pulmonary, critical care, and sleep medicine globally to the next level.

The CHEST Foundation has stimulated important opportunities for research, increased the ability for younger members to attend meetings



Dr. Clayton T. Cowl

and actively engage in CHEST activities, and provided valuable information to patients in a language they can understand. Thanks to advances in technology, there are improved platforms for communicating with our membership and for delivering education in novel and more effective ways than ever before. We plan to double down on our strategic focus of utilizing innovation and new technologies to lead trends in education, influence health-care improvements for our patients and their families, and to deliver the latest in medical education to clinicians and investigators worldwide.

What are some challenges facing CHEST, and how will you address these challenges?

Many of our members are facing challenges in their practices – both domestically and internationally. Industry and employer-based sponsorship to attend meetings has declined, travel

remains expensive, and time away from the practice has become more and more difficult for a variety of reasons. Our members are being challenged with greater regulatory and administrative burdens and are bombarded with the demands of work overload.

In addition to working with other organizations to identify workplace burnout and, more importantly, to offer better solutions, we are focused on leveraging a variety of new technologies to bring our CHEST brand of quality education to all of our members, regardless of location, and to do so in a way that best suits individual needs.

The traditional model of attending a large meeting comprised solely of didactic presentations is, frankly, becoming outdated. CHEST will continue to “tip the apple cart” of worn out educational delivery methods and look toward innovating courses that are more accessible, more effective and relevant, more affordable, and more fun.

And finally, what is your charge to the members and new Fellows of CHEST?

We have each been blessed with the opportunity to serve patients and their families in their times of need. Let's not forget that privilege as we deliver care each and every day. The word “doctor” comes from an agentive noun of the Latin verb *docere* (“to teach”). Regardless of where you practice, what your role is in the health-care paradigm, or whether your contribution is directly with patients or indirectly through research, education, or administration, we are all teachers in various ways to various people.

That's why the American College of Chest Physicians (CHEST) needs to listen to your needs, cultivate your collective wisdom, and continue to be the leading organization within our specialties for delivering medical education and, ultimately, for providing outstanding care and compassion to our patients.

This month in the journal **CHEST**[®]

Editor's picks

**BY RICHARD S. IRWIN,
MD, MASTER FCCP**

Editor in Chief

ORIGINAL RESEARCH

A Pilot Feasibility Study in Establishing the Role of Ultrasound-Guided Pleural Biopsies in Pleural Infection (The AUDIO Study).

By Dr. I. Psallidas, et al.

COMMENTARY

Sleep Apnea Morbidity: A Consequence of Microbial-Immune Cross-Talk?

By Dr. N. Farre, et al.



EVIDENCE-BASED MEDICINE

Treatment of Interstitial Lung Disease-Associated Cough: CHEST Guideline and Expert Panel Report.

By Dr. S. S. Birring, et al.

New updates to afib guidelines

The American College of Chest Physicians announced updates to the evidence-based guidelines on antithrombotic therapy for atrial fibrillation. The guideline panel submitted the manuscript, Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report, for publication in the journal *CHEST*[®].

Key recommendations and shifts from previous guidelines include:

- For patients with atrial fibrillation without valvular heart disease, including those with paroxysmal atrial fibrillation who are at low risk of stroke (eg, CHA2DS2VASc score of 0 in males or 1 in females), we suggest no antithrombotic therapy.
- For patients with a single non-sex CHA2DS2VASc stroke risk factor, we suggest oral anticoagulation rather than no therapy, aspirin or combination therapy

with aspirin and clopidogrel.

- For those at high risk of stroke, we recommend oral anticoagulation rather than no therapy, aspirin or combination therapy with aspirin and clopidogrel.
- Where we recommend or suggest in favor of oral anticoagulation, we suggest using a novel oral anticoagulant (NOAC) rather than adjusted-dose vitamin K antagonist therapy. With the latter, it is important to aim for good quality anticoagulation control with a time in therapeutic range (TTR) >70%.
- Attention to modifiable bleeding risk factors should be made at each patient contact, and HAS-BLED score should be used to assess the risk of bleeding where high-risk patients (≥3) can be identified for earlier review and follow-up visits.

The complete guideline article is free to view in the Online First section of the journal *CHEST*.

Upcoming CPT® changes

BY MIKE NELSON, MD, FCCP
CHEST Physician Editorial Board Member

Pulmonary, critical care, and sleep physicians often provide services to patients, as well as consultative services to other health-care professionals, without a patient being present. This can be done via telephone or electronic (internet or electronic health record) commu-



Dr. Michael E. Nelson

nications. Many are not aware that Current Procedural Terminology (CPT®) codes were published to describe and define the work involved in these services. In 2019, there will be additional CPT® codes available for health-care workers to use for these non-face-to-face services.

Telephone services are reported using CPT® codes **99441-99443** and may be used for evaluation and management (E/M) services provided by telephone for an established patient that do not result in a patient visit within the next 24 hours or are associated with an E/M visit from the last 7 days.

99441 Telephone evaluation and management service by a physician or other qualified health-care professional who may report evaluation and management services provided to an established patient, parent, or guardian not originating from a related E/M service provided within the previous 7 days nor leading to an E/M service or procedure within the next 24 hours or soonest available appointment; 5-10 minutes of medical discussion

99442 11-20 minutes of medical discussion

99443 21-30 minutes of medical discussion

These codes may not be reported by a provider more frequently than every 7 days. The details of the service should be documented in the medical record.

If the E/M service is prompted

by an online patient request, then CPT® code **99444** can be used.

99444 Online evaluation and management service provided by a physician or other qualified health

care professional who may report evaluation and management services provided to an established patient or guardian, not originating from a related E/M service provided within

the previous 7 days, using the internet or similar electronic communications network.

This code may be reported only every 7 days and cannot be related

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to a previous E/M evaluation in the last 7 days or to a previous surgical procedure. The service includes all of the communication (eg, related telephone calls, prescription provision, laboratory orders) pertaining to the online patient encounter.

There are also CPT® codes for

interprofessional telephone/ internet/ electronic health record consultations. These codes are used when one health-care provider requests the opinion and/or treatment advice of another provider (consultant) for either a new or established patient without face-to-face contact between

the patient and the consultant.

99446 Interprofessional telephone/Internet/electronic health record assessment and management service provided by a consultative physician, including a verbal and written report to the patient's treating/requesting physician or other

qualified health care professional; 5-10 minutes of medical consultative discussion and review.

99447 11-20 minutes of medical consultative discussion and review

99448 21-30 minutes of medical consultative discussion and review

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99449 31 minutes or more of medical consultative discussion and review

These codes are not used if the consultant has seen the patient in a face-to-face encounter within the last 14 days or the consultation results

in a transfer of care or other face-to-face service with the consultant within the next 14 days. In addition, greater than 50% of the service time reported must be devoted to the medical consultative verbal or internet discussion. The request and reason for telephone/internet/

electronic health record consultation by the requesting health-care professional should be documented in the patient's medical record. After an oral report from the consultant is provided to the treating/requesting physician, a written report should be documented in the medical record.

Consultations of less than 5 minutes should not be reported.

As noted, CPT[®] codes **99446-49** require an oral and written report. A new code is added for 2019.

99451 Interprofessional telephone/Internet/electronic health record assessment and management service provided by a consultative physician, including a written report to the patient's treating/requesting physician or other qualified health care professional, 5 minutes or more of medical consultative time.

CPT[®] code **99451** describes a consultative service lasting more than 5 minutes and requires only a written report to the requesting physician. This was added recognizing that oral communications do not always occur between health-care professionals and may facilitate consultative services in geographic areas with no specialists available.

99452 Interprofessional telephone/internet/electronic health record referral service(s) provided by a treating/requesting physician or other qualified health-care professional, 30 minutes.

CPT[®] code **99452** is reported for 16-30 minutes preparing for the referral and/or communicating with a consultant. If more than 30 minutes is spent by the treating/requesting health-care provider, then one would use a prolonged services code (**99358-59**).

As with all coding and billing issues, review the CPT[®] manual for parentheticals that describe coding rules not included in the code description. In addition, not all CPT[®] codes are paid by all providers. Knowledge of payer policies is, therefore, important for appropriate reimbursement.

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In memoriam

CHEST has been notified of the following deaths. We extend our sincere condolences.

Adriaan Manten, PhD,
FCCP (2018)

Praveen Mathur, MD,
FCCP (2018)

Carol Marcus, MD
(2018)

Donald G. Burns, DO,
FCCP (2018)

Stanley M. Cassan, MD, PhD
(2018)

CRITICAL CARE COMMENTARY

ECMO for ARDS in the modern era

BY CARA AGERSTRAND, MD

Extracorporeal membrane oxygenation (ECMO) has become increasingly accepted as a rescue therapy for severe respiratory failure from a variety of conditions, though most commonly, the acute respiratory distress syndrome (ARDS) (Thiagarajan R, et al. *ASAIO*. 2017;63[1]:60). ECMO can provide respiratory or cardiorespiratory support for failing lungs, heart, or both.

The most common ECMO configuration used in ARDS is venovenous ECMO, in which blood is withdrawn from a catheter placed in a central vein, pumped through a gas exchange device known as an oxygenator, and returned to the venous system via another catheter. The blood flowing through the oxy-

genator is separated from a continuous supply of oxygen-rich sweep gas by a semipermeable membrane, across which diffusion-mediated gas exchange occurs, so that the blood exiting it is rich in oxygen and low in carbon dioxide.

As venovenous ECMO functions in series with the native circulation, the well-oxygenated blood exiting the ECMO circuit mixes with poorly oxygenated blood flowing through the lungs. Therefore, oxygenation is dependent on native cardiac output to achieve systemic oxygen delivery (Figure 1).



DR. AGERSTRAND

ECMO been used successfully in adults with ARDS since the early 1970s (Hill JD, et al. *N Engl J Med*. 1972;286[12]:629-34), but until recently, was limited to small

Initiation of ECMO may be reasonable prior to implementation of standard of care therapies, in order to permit safe transfer to an experienced center from a center not able to provide them.

numbers of patients at select global centers and associated with a high-risk profile. In the last decade, however, driven by improvements in ECMO circuit components making the device safer and easier to

use, encouraging worldwide experience during the 2009 influenza A (H1N1) pandemic (Davies A, et al. *JAMA*. 2009;302[17]:1888-95), and publication of the Efficacy and Economic Assessment of Conventional Ventilatory Support versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR) trial (Peek GJ, et al. *Lancet*. 2009;374[9698]:1351-63), ECMO use has markedly increased.

Despite its rapid growth, however, rigorous evidence supporting the use of ECMO has been lacking. The CESAR trial, while impressive in execution, had methodological issues that limited the strength of its conclusions. CESAR was a pragmatic trial that randomized 180 adults with severe respiratory failure from multiple etiologies to conventional

Continued on following page

National Board of Echocardiography offers board exam

BY PAUL H. MAYO, MD, FCCP;
AND NITIN PURI, MD, FCCP

Due to significant interest in the pulmonary/critical care community, the National Board of Echocardiography (NBE) has opened registration for a board examination as a requirement for national level certification in advanced critical care echocardiography (ACCE). The examination has been developed by the National Board of Medical Examiners; CHEST and the other professional societies are well represented on the writing committee. The first examination is scheduled to be given on January 15, 2019.

The board of the NBE will be the final arbiter for other requirements for certification. We anticipate that these will be available in 2019.

A few essential questions about the certification:

1. Who will be eligible for certification in ACCE?

The policy of the NBE is that any licensed physician may take the examination. Passing the examination confers testamur status, which is only one of several requirements for certification. The board of the NBE will make the final decision as to how to define the clinical background of the candidate that will be required for certification.

2. What will be the requirements for demonstration of competence at image acquisition for ACCE?

Competence at ACCE requires that the intensivist be expert at image acquisition of a comprehensive image set. The board of the NBE will make the final decision as to what constitutes a full ACCE image set, how many studies must be performed by the candidate, and how the studies will be documented. Regarding the latter question, it is likely that there will be a need for identification of qualified mentors to guide the candidate through the process of demonstrating competence in image acquisition.

3. What resources exist to learn more about the examination?

For some suggestions regarding mastery of the cognitive base, Dr. Yonatan Greenstein has set up an independent website that has recommendations about study material and an example of the full ACCE image set (advancedcriticalcareecho.org). The NBE website has a list of subjects that will be covered in the examination. In addition to passing the examination, there will be other elements required for ACCE certification. The NBE has not yet made final decision on the additional requirements. As soon as they are available, they will be posted on the

NBE website (echoboards.org).

There is keen interest amongst fellows and junior attendings in the NBE certification who are already competent in whole body ultrasonography. They see ACCE as a natural and necessary extension of their scope of practice, as a means of better helping their critically ill patients, and as a means of acquiring a unique skill that defines them as having a special skill compared with other intensivists. A smaller group of senior attending intensivists are primarily motivated by a well-defined practice-related need of skill at ACCE and/or a strong perception that knowledge of ACCE may directly improve their ability to care for the critically ill patient. Interest in certification extends across the various specialties that provide critical care services. The NBE has indicated that there has been a strong showing of registrations for the examination thus far.

We recommend that candidates for certification consider that passing the examination should be the priority. Collection of the image set may occur in parallel, as the two will complement each other. Preparation for the examination requires intensive study of the cognitive base of ACCE and mastery of image interpretation.

To aid in preparation for the ACCE examination, CHEST is offering a comprehensive review

course, Advanced Critical Care Echocardiography Board Review Exam Course, being held at the CHEST Innovation, Simulation, and Training Center, December 7-8, 2018, in Glenview, Illinois.

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management or transfer to an experienced, ECMO-capable center. CESAR met its primary outcome of improved survival without disability in the ECMO-referred group (63% vs 47%, relative risk [RR] 0.69; 95% confidence interval [CI] 0.05 to 0.97, $P=.03$), but not all patients in that group ultimately received ECMO. In addition, the use of lung protective ventilation was significantly higher in the ECMO-referred group, making it difficult to separate its benefit from that of ECMO. A conservative interpretation is that CESAR showed the clinical benefit of treatment at an ECMO-capable center, experienced in the management of patients with severe respiratory failure.

Not until the release of the Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA) trial earlier this year (Combes A, et al. *N Engl J Med*. 2018;378[21]:1965-75), did a modern, randomized controlled trial evaluating the use of ECMO itself exist. The EOLIA trial addressed the limitations of CESAR and randomized adult patients with early, severe ARDS to conventional, standard of care management that included a protocolized lung protective strategy in the control group vs immediate initiation of ECMO combined with an ultra-lung protective strategy (targeting end-inspiratory plateau pressure ≤ 24 cmH₂O) in the intervention group. The primary outcome was all-cause mortality at

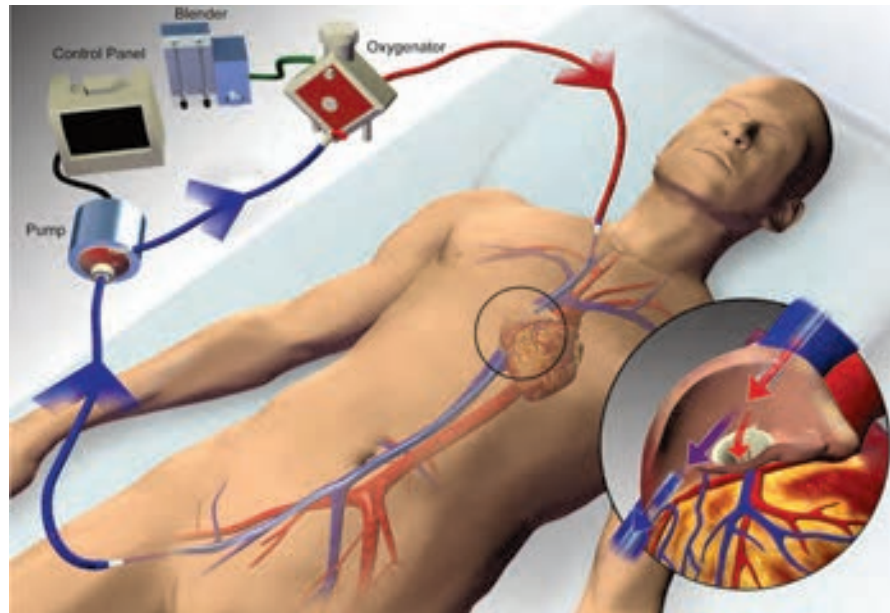


Figure 1. Two-site venovenous extracorporeal membrane oxygenation (ECMO). With permission from Agerstrand C, et al. ECMO for adult respiratory failure: current use and evolving applications. *ASAIO*. 2014;60(3):255-262.

60 days. Of note, patients enrolled in EOLIA met entry criteria despite greater than 90% of patients receiving neuromuscular blockade and around 60% treated with prone positioning at the time of randomization (importantly, 90% of control group patients ultimately underwent prone positioning).

EOLIA was powered to detect a 20% decrease in mortality in the ECMO group. Based on trial design and the results of the fourth interim analysis, the trial was stopped for futility to reach that endpoint after enrollment of 249 of a maximum 331 patients. Although a 20% mortality reduction was not achieved, 60-day mortality was notably lower in the ECMO-treated group (35% vs 46%, RR 0.76, 95% CI 0.55 to 1.04, $P=.09$). The key secondary outcome of risk of treatment failure (defined as death in the ECMO group and death or crossover to ECMO in the control group) favored the ECMO group with a RR for mortality of 0.62 (95% CI, 0.47 to 0.82; $P<.001$), as did other secondary endpoints, such as days free of renal and other organ failure.

A major limitation of the trial was that 35 (28%) of control group patients ultimately crossed over to ECMO, which diluted the effect of ECMO observed in the intention-to-treat analysis. Crossover occurred at clinician discretion an average of 6.5 days after randomization and after stringent criteria for crossover was met. These patients were incredibly ill, with a median oxygen saturation of 77%, rapidly worsening inotropic scores, and lactic acidosis; nine individuals had already suffered cardiac arrest, and six had received ECMO as part of extracorporeal cardiopulmonary

resuscitation (ECPR), the initiation of venoarterial ECMO during cardiac arrest in attempt to restore spontaneous circulation. Mortality was considerably worse in the crossover group than in conventionally managed cohort overall, and, notably, 33% of patients crossed over to ECMO still survived.

In order to estimate the effect of ECMO on survival times if crossover had not occurred, the authors performed a post-hoc, rank-preserving structural failure time analysis. Though this relies on some assessment regarding the effect of the treatment itself, it showed a hazard ratio for mortality in the ECMO group of 0.51 (95% CI 0.24 to 1.02, $P=.055$). Although the EOLIA trial was not positive by traditional interpretation, all three major analyses and all secondary endpoints suggest some degree of benefit in patients with severe ARDS managed with ECMO.

Importantly, ECMO was well tolerated (at least when performed at expert centers, as done in this trial). There were significantly more bleeding events and cases of severe thrombocytopenia in the ECMO-treated group, but massive

hemorrhage, ischemic and hemorrhagic stroke, arrhythmias, and other complications were similar.


Where do we go from here?

Based on the totality of information, it is reasonable to consider ECMO for cases of severe ARDS not responsive to conventional measures, such as a lung protective ventilator strategy, neuromuscular blockade, and prone positioning. Initiation of ECMO may be reasonable prior to implementation of standard of care therapies, in order to permit safe transfer to an experienced center from a center not able to provide them.

Two take-away points: First, it is important to recognize that much of the clinical benefit derived from ECMO may be beyond its ability to normalize gas exchange and be due, at least in part, to the fact that ECMO allows the enhancement of proven lung protective ventilatory strategies. Initiation of ECMO and the “lung rest” it permits reduce the mechanical power applied to the injured alveoli and may attenuate ventilator-induced lung injury, cytokine release, and multiorgan failure that portend poor clinical outcomes in ARDS. Second, ECMO in EOLIA was conducted at expert centers with relatively low rates of complications.


It is too early to know how the critical care community will view ECMO for ARDS in light of EOLIA as well as a growing body of global ECMO experience, or how its wider application may impact the distribution and organization of ECMO centers. Regardless, of paramount importance in using ECMO as a treatment modality is optimizing patient management both prior to and after its initiation.

Dr. Agerstrand is Assistant Professor of Medicine, Director of the Medical ECMO Program, Columbia University College of Physicians and Surgeons, New York-Presbyterian Hospital.



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PULMONARY PERSPECTIVES®

The importance of diversity and inclusion in medicine

BY DEMONDES HAYNES, MD, FCCP

Diversity

There is growing appreciation for diversity and inclusion (DI) as drivers of excellence in medicine. CHEST also promotes excellence in medicine. Therefore, it is intuitive that CHEST promote DI. Diversity encompasses differences in gender, race/ethnicity, vocational training, age, sexual orientation, thought processes, etc.

Academic medicine is rich with examples of how diversity is critical to the health of our nation:

- Diverse student populations have been shown to improve our learners' satisfaction with their educational experience.
- Diverse teams have been shown to be more capable of solving complex problems than homogenous teams.
- Health care is moving toward a team-based, interprofessional model that values the contributions of a range of providers' perspectives in improving patient outcomes.
- In biomedical research, investigators ask different research questions based on their own background and experiences. This implies that finding solutions to diseases that affect specific populations will require a diverse pool of biomedical researchers.

- Faculty diversity as a key component of excellence for medical education and research has been documented.

Diversity alone doesn't drive inclusion. Noted diversity advocate, Verna Myers, stated, "Diversity is being invited to the party. Inclusion is being asked to dance." In my opinion, diversity is the commencement of work, but inclusion helps complete the task.

Inclusion

An inclusive environment values the unique contributions all members bring. Teams with diversity of thought are more innovative as individual members with different backgrounds and points of view bring an extensive range of ideas and creativity to scientific discovery and decision-making processes. Inclusion leverages the power of our unique differences to accomplish our mutual goals. By valuing everyone's perspective, we demonstrate excellence.

I recommend an article from the Harvard Business Review (*HBR* Feb 2017). The authors suggest several ways to promote inclusiveness: (1) ensuring team members speak up and are heard; (2) making it safe to propose novel ideas; (3) empowering team members to make decisions; (4) taking advice and implementing feedback; (5) giving actionable feed-



DR. HAYNES

back; and (6) sharing credit for team success. If the team leader possesses at least three of these traits, 87% of team members say they feel welcome and included in their team; 87% say they feel free to express their views and opinions; and 74% say they feel that their ideas are heard and recognized. If the team leader possessed none of

these traits, those percentages dropped to 51%, 46%, and 37%, respectively. I believe this concept is applicable in medicine also.

Sponsors

What can we do to advance diversity and inclusion individually and in our individual institutions? A sponsor is a senior level leader who advocates for key assignments, promotes for and puts his or her reputation on the line for the protégé's advancement. This invigorates and drives engagement. One key to rising above the playing field for women and people of color is sponsorship. Being a sponsor does not mean one would recommend someone who is not qualified. It means one recommends or supports those who are capable of doing the job but would not other-

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Who Should Attend?

Intensive care providers, pulmonary and critical care physicians, advanced practice providers (NPs and PAs), ECMO specialists (RN, RT), cardiothoracic surgeons, trauma surgeons, cardiologists, and any provider who cares for patients with severe respiratory or cardiac failure are encouraged to attend.



Extracorporeal Support for Respiratory and Cardiac Failure in Adults

December 7-9, 2018 | CHEST Innovation, Simulation, and Training Center

Through live lectures and hands-on workshops, this course is designed for intensive care providers who want to become better acquainted with extracorporeal membrane oxygenation (ECMO).

Led by experts from high volume ECMO centers, this course consists of a mix of lectures and high-fidelity workshops focusing on an introduction to veno-arterial (VA) ECMO for refractory cardiac failure, cardiopulmonary failure, extracorporeal CPR (eCPR), and guidance for starting and maintaining new ECMO programs.



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CHEST Foundation – designated as a Combined Federal Campaign-approved charity



THE CHEST Foundation was recently designated as a Combined Federal Campaign-approved charity! The federal campaign started on September 10 and runs through January 11, 2019. If you are a federal employee organizing your workplace giving, you can easily choose the CHEST Foundation as your designated charity! Simply list our CFC number when designating your selected charity!

CFC Number: 24565

To set up your CFC account, follow these easy steps outlined below:

1. Visit <https://cfcgiving.opm.gov/welcome>
2. From the welcome page, select “sign up now,” and fill out the required information if you do not have an ac-

count. If you do have an account, simply log in using the email address tied to your CFC account and your password, and skip to step 6.

3. After your account is set up, the CFC will send you an email to the address you provided along with a verification pin number. Select the “CLICK HERE to enter your PIN” option from the verification email, and enter the provided pin on the page provided by the link.

4. On the next page, you will create your security questions to log back into your account, should you lose your password. Select “Save Changes” at the bottom of the page when you are ready to move on.

5. Next, you’ll be asked to fill out some personal information about

yourself as a donor, such as your full name, and which department of the federal government you work for. Choose “Save Changes” at the bottom of the page when you are done.

6. Upon completing the profile page (or logging into your account), you will be directed to the welcome page. Select the “Pledge Now” button, located in the center of the page.

7. The next page will ask you questions about the charity you would like to support. Enter the CHEST Foundation’s CFC number: 24565, and click “Search for Charities” to be directed to the next page.

8. Select the “add” button next to the CHEST Foundation’s listing. Then click the “checkout” button

that appears in the pop-up window.

9. Fill out the requested information regarding your pledge amount, your pledge frequency, and your annual pledge amount, then select the “Continue with your pledge” option at the bottom of the page.

10. On this final page, you can review your pledge amount and review a brief attestation agreement. After reviewing, check the “I confirm” checkbox, then click “submit pledge.”

That’s it!

Thank you for supporting the CHEST Foundation’s mission-based programming supporting patient education materials, clinical research grants, and community service initiatives.

Continued from previous page

wise be given the opportunity.

Ask yourself: Have I served as a sponsor? What would prevent me from being a sponsor? Do I believe in this concept?

Cause for alarm

Numerous publications have recently discussed the crisis of the decline of black men entering medicine. In 1978, there were 1,410 black male applicants to medical school, and in 2014, there were 1,337. Additionally, the number of black male matriculants to medical school over more than 35 years has not surpassed the 1978 numbers. In 1978, there were 542 black male matriculants, and in 2014, there were 515 (*J of Racial and Ethnic Health Disparities*. 2017, 4:317-321). This report is thorough and insightful and illustrates the work that we must do to help improve this situation.

Dr. Marc Nivet, Association of American Medical Colleges (AAMC) Chief Diversity Officer, stated “No other minority group has experienced such declines. The inability to find, engage, and develop candidates for careers in medicine from all members of our society limits our ability to improve health care for all.” I recommend you read the 2015 AAMC publication entitled: *Altering the Course: Black Males in Medicine*.

Health-care disparities

Research suggests that the overall health of Americans has improved; however, disparities continue to persist among many populations within the United States. Racial and ethnic minority populations have poorer access to care and worse outcomes than their white counterparts. Approximately 20% of the nation living in rural areas is less likely than those living in urban areas to receive preventive care and more likely to experience language barriers.

Individuals identifying as lesbian, gay, bisexual, or transgender are likely to experience discrimi-

nation in health-care settings. These individuals often face insurance-based barriers and are less likely to have a usual source of care than patients who identify as straight.

A 2002 report by the Institute of Medicine entitled: *Unequal Treatment: What Healthcare Providers Need to Know about Racial and Ethnic Disparities in Healthcare* is revealing. Salient information reported is: It is generally accepted that a diverse workforce is a key component in the delivery of quality, competent care throughout the nation. Physicians from racial and ethnic backgrounds typically underrepresented in medicine are significantly more likely to practice primary care than white physicians and are more likely to practice in impoverished and medically underserved areas. Diversity in the physician workforce impacts the quality of care received by patients. Race concordance between patient and physician results in longer visits and increased patient satisfaction, and language concordance is positively associated with adherence to treatment among certain racial or ethnic groups.

Improving the patient experience or quality of care received also requires attention to education and training on cultural competence. By weaving together a diverse and culturally responsive pool of physicians working collaboratively with other health-care professionals, access and quality of care can improve throughout the nation.

CHEST cannot attain more racial diversity in our organization if we don’t have this diversity in medical education and training. This is why CHEST must be actively involved in addressing these issues.

Unconscious bias

Despite many examples of how diversity enriches the quality of health care and health research, there is still much work to be done to address the human biases that impede our ability to benefit from diversity in medicine. While academic medicine has made progress toward addressing overt dis-

crimination, unconscious bias (implicit bias) represents another threat. Unconscious bias describes the prejudices we don’t know we have. While unconscious biases vary from person to person, we all possess them. The existence of unconscious bias in academic medicine, while uncomfortable and unsettling, is a reality. The AAMC developed an unconscious bias learning lab for the health professions and produced an oft-cited video about addressing unconscious bias in the faculty advancement, promotion, and tenure process. We must consider this and other ways in which we can help promote the acknowledgement of unconscious bias. Many CHEST staff have undergone unconscious bias training, and I recommend it for all faculty in academic medicine.

Summary

Diversity and inclusion in medicine is of paramount importance. It leads to better patient care and better trainee education and will decrease health-care disparities. Progress has been made, but there is more work to be done.

CHEST is supportive of these efforts and has worked on this previously and with a renewed push in the past 2 years with the DI Task Force initially and, now, the DI Roundtable, which has representatives from each of the standing committees, including the Board of Regents. This roundtable group will help advance the DI initiatives of the organization. I ask that each person reading this article consider what we as individuals can do in helping make DI in medicine a priority.

Dr. Haynes is Professor of Medicine at The University of Mississippi Medical Center in Jackson, MS. He is also the Executive Vice Chair of the Department of Medicine. At CHEST, he is a member of the Training and Transitions Committee, Scientific Program Committee, former chair of the Diversity and Inclusion Task Force, and is the current chair of the Diversity and Inclusion Roundtable.

CHEST NETWORKS

EBV therapy. CFTR modulators. LC diagnosis with multiple tumor nodules.

Interventional Chest/ Diagnostic Procedures Endobronchial valve therapy receives FDA approval for bronchoscopic LVR

Lung volume reduction surgery (LVRS) is an established approach to improve exercise capacity and lung function in patients with heterogeneous emphysema and may confer survival benefit in patients with apical-predominant disease (Fishman, et al. *N Engl J Med.* 2003;348[21]:2059). Despite this, LVRS case numbers remain low due to patient and procedural morbidity. Bronchoscopic alternatives for LVRS have advanced considerably over the last decade with endobronchial valve (EBV) therapy emerging as a viable option for select subsets of patients with heterogeneous emphysema. Endobronchial valves are removable devices placed in segmental/subsegmental airways, which allow efflux of air during exhalation but close during inspiration, resulting in distal atelectasis in the absence of collateral ventilation.

The LIBERATE study, a multi-center randomized controlled trial demonstrated improvement in FEV₁ $\geq 15\%$ in 48% of patients after EBV placement compared with 17% of patients receiving standard medical therapy has resulted in FDA approval (Criner G, et al. *Am J Respir Crit Care Med.* 2018 May 22. doi: 10.1164/rccm.201803-0590OC [Epub ahead of print]). Patients with EBV had improved subjective dyspnea scores, residual volume, and 6-minute walk distance; however, the pneumothorax rate was 27%.

All study patients with EBV underwent bronchoscopic evaluation for collateral ventilation using a proprietary digital system, which measures expiratory airflow in target airways to establish the presence of collateral ventilation. Previous data have demonstrated improved transplant-free survival when implanted EBVs result in atelectasis of the target lobe, which requires intact interlobar fissures (Garner, et al. *Am J Respir Crit Care Med.* 2016;194[4]:519). Ongoing clinical trials are attempting

to clarify the role of EBV therapy in different phenotypes of COPD, including patients with homogenous emphysema. Long-term follow-up data will be important in determining the broader implementation of bronchoscopic lung volume reduction moving forward.

Vivek Murthy, MD
Jason A. Akulian, MD, FCCP
Steering Committee Members



DR. BHARGAVA

Established CF treatments include pulmonary and nutritional interventions. CFTR modulators are recent novel therapies that improve the function of CFTR and

target the basic defect. Two types of modulator drugs (potentiators and correctors) have been developed with effectiveness depending upon the kind of CF mutation the person has.

CFTR potentiators, such as Kalydeco® (ivacaftor monotherapy), increase the likelihood that the CFTR channel will transport ions through the cell membrane, ie, they increase the channel's "open probability." Kalydeco has been approved for patients 12 months or older with mutations that result in partial CFTR protein function in the cell membrane. CFTR correctors, such as lumacaftor and tezacaftor, increase the amount of normal or mutated

Pediatric Chest Medicine CFTR modulators

Cystic fibrosis (CF) is a progressive genetic disorder resulting in multiorgan disease with progressive respiratory decline. CF is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. This codes for the CFTR anion channel and contributes to the movement of salt in and out of the cell. CFTR dysfunction leads to thickened secretions in the lungs and other organs, such as the gut and pancreas. This leads to more lung infections and other organ dysfunction that ultimately leads to premature death.

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CFTR protein that gets transported, increasing the amount of CFTR protein on the cell surface. Combination drugs such as Orkambi® (lumacaftor/ivacaftor) for patients 2 years and older, and Symdeko™ (tezacaftor/ivacaftor) for patients 12 years and older, are considered in patients homozygous for the F508del mutation.

Sumit Bhargava, MBBS, FCCP
Steering Committee Member

Pulmonary Physiology, Function, and Rehabilitation Wildfires, particulate matter, and lung function

In the last 3 decades, human-caused climate change contributed to wildfires in an additional 4.2 million hectares (approximately 10 million acres) of land across the western US alone. Human impact on climate is responsible for nearly doubling the expected wildfire area (Abatzoglou, et al. *PNAS*. 2016;113[42]:11770). Year 2017 saw the most destructive wildfires in California recorded to date, and over \$2 billion dollars was spent by the US Forest Service, the most-expensive on record. Besides the devastating effects on the forestry and nearby communities, wildfires also generate a large amount of particulate matter (PM). In western US, wildfires contributed to 71.3% of total PM_{2.5} on days exceeding regulatory PM_{2.5} standards during 2004-2009 (Liu et al. *Clim Change*. 2016;138[3]:655). Acute PM exposure is associated with respiratory health effects, such as exacerbation of asthma and COPD, increased ED visits and hospitalization for pneumonia, and increased mortality. Chronic PM_{2.5} exposure may also affect lung function. Cross-shift and cross-season FEV₁ declined by 0.150 L and 0.104 L, respectively in forest firefighters (Betchley, et al. *Am. J Ind Med*. 1997;31[11]:503). The Children's Health Study conducted in California found that subjects who were exposed to the highest level of exposure to PM_{2.5} were five times more likely to have an FEV₁ less than 80% of expected FEV₁ when they reached 18 years of age than subjects exposed to the lowest level of PM_{2.5} (Gauderman et al. *N Engl J Med*. 2004;351[11]:1057). Clinicians should educate patients and the public how to protect our environment and, when wildfires occur, how to protect themselves from exposure to PM.

Thomas W. DeCato, MD
Fellow-in-Training Committee
Member
Yuh-Chin T. Huang, MD, FCCP
Steering Committee Member



DR. BALASUBRAMANIAN



DR. ELWING

Pulmonary Vascular Disease Small increases in pulmonary pressures—big impact

Pulmonary hypertension (PH) is a progressive, life-limiting pulmonary vascular disease that is diagnosed hemodynamically by right-sided heart catheterization (RHC) and defined by a mean pulmonary artery pressure (mPAP) >25 mm Hg (Hooper MM, et al. *JACC*. 2013;62[25 Suppl]:D42). The impact of PH on survival both in its "pure" form, pulmonary arterial hypertension, and in the setting of underlying cardiopulmonary disease, is well established. However, the clinical relevance of mildly elevated mPAP, defined as mPAP between 18 and 24 mm Hg, has been unclear until recently. Two large cohort studies have suggested that mild increases in mPAP are clinically relevant. A large retrospective analysis of hemodynamic data from 21,727 US veterans found mildly increased mPAP (19-24 mm Hg) was associated with increased hospitalization and decreased survival (Maron, et al. *Circulation*. 2016;133[13]:1240). While this population was skewed toward elderly men, a study from Vanderbilt University that included equal numbers of men and women showed similar results. Patients with mPAP 19-24 mm Hg experienced incrementally increased mortality (HR:1.31, *P*=.001). Importantly, in the subset of patients who underwent a repeat RHC in follow-up, 61% developed progressive increases of pulmonary pressures (>25 mm Hg) on follow-up RHC suggesting that the disease process may progress in a substantial proportion of patients (Assad, et al. *JAMA Cardiol*. 2017;2[1]:1361). Combined with prior data from smaller cohorts, these studies highlight the impact of mildly increased pulmonary pressures on outcomes. Given the dearth of available data regarding interventions for these patients, there is an urgent need to study to role of specific therapy for mildly elevated pulmonary pressures.

Vijay Balasubramanian, MD,
FCCP
Steering Committee Member
Jean Elwing, MD, FCCP
Steering Committee Vice-Chair

Thoracic Oncology Multiple tumor nodules in lung cancer diagnosis

Low dose CT (LDCT) scan screening for lung cancer is a recommended preventive modality for adults with a significant smoking history (Mayer et al. *Ann Int Med*. 2014;160[5]:330). The screening approach aims to identify adults at significant risk for lung cancer. The goal is to discover lung cancers at low stage with benign mediastinal nodes for optimal treatment and potential for cure. In a minority, but significant number of cases, the LDCT demonstrates multiple lung nodules or masses confounding the attempt to adequately stage the tumor. Two tumors representing a primary cancer and separate malignant spread, namely, intra-pulmonary metastases, in the same lobe, different ipsilateral lobe, or contralateral lobe would be staged, respectively, as T3, T4, or M1a (Detterbeck et al. *CHEST*. 2013;143[5]:e191S). Clearly, if the two tumors are separate unique primary cancers, independent of one another, then at best they would be considered as multiple T1 tumors. The treatment modalities of and clinical survival outcomes for these multiple conditions would be markedly different.

The identification of additional tumors may be synchronous (at the same time of the primary discovery) or metachronous (at a later time than the primary discovery). The approach is basically the same. Two tumors with different histologic types, or having separate in-situ squamous cell carcinoma patterns, or disparate immunohistochemical or molecular expressions, or different genomic profiles or driver mutations may be considered as separate distinct primary malignancies (Detterbeck et al. *J Thorac Oncol*. 2016;11[5]:639; Nicholson et al. *J Thorac Oncol*. 2017;13[2]:205). Separate foci of ground-glass opacities with small solid central component indicative of minimally invasive adenocarcinoma may be designated as the highest T-stage. These cited and more challenging cases should be presented to a lung cancer tumor board with multiple specialties represented for analysis and judgment. The approach to diagnostic decision-making and clinical management should involve the expertise of all specialties in the lung cancer patient care team.

Arnold M. Schwartz, MD, PhD,
FCCP
Steering Committee Member



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