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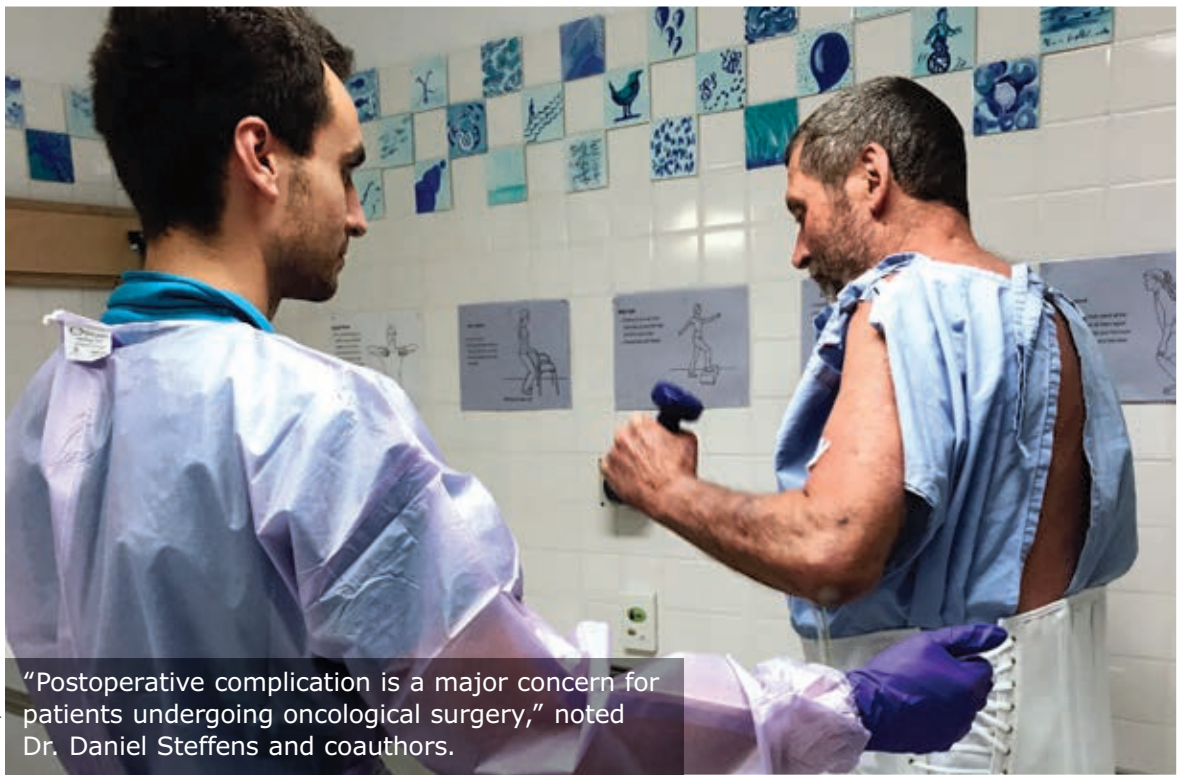

Courtesy Dr. Daniel Steffens

"Postoperative complication is a major concern for patients undergoing oncological surgery," noted Dr. Daniel Steffens and coauthors.

Preoperative exercise cuts postop lung resection complications

BY BIANCA NOGRADY
Frontline Medical News

Patients undergoing surgery for lung cancer may benefit from a program of preoperative exercise, with a systematic review suggesting it reduces postoperative complications and duration of hospital stay.

The review and meta-analysis, published in the February British Journal of Sports Medicine, looked at the impact of preoperative exercise in patients undergoing surgery for a range of cancers.

Their review of 13 interventional trials, involving 806 patients and six tumor types, found the postoperative benefits of exercise were evident only in patients undergoing lung resection.

Data from five randomized controlled trials and one quasirandomized trial in lung cancer patients showed a significant 48% reduction in postoperative complications, and a significant mean reduction of 2.86 days in hospital stay among patients undergoing lung resection, compared with controls.

"Postoperative complication is a major concern for patients undergoing oncological surgery," wrote Daniel Steffens, PhD, from the Surgical Outcomes Research Centre at the Royal Prince Alfred Hospital, Sydney, and his coauthors. They suggested the benefits for patients undergoing lung resection were significant

CANCER SURGERY PATIENTS HELPED // *continued on page 5*

OSA may provide cardioprotection

Cardiac troponin-I levels lower in sleep apnea patients

BY MADHU RAJARAMAN
Frontline Medical News

FROM THE JOURNAL *CHEST*® ▪ The presence of obstructive sleep apnea (OSA) may have a protective effect in patients with acute coronary syndromes, according to researchers.

In a study of 127 patients presenting with acute coronary syndromes (ACS), median peak cardiac troponin-I (cTn-I) values were significantly higher in patients without obstructive sleep apnea, compared with OSA patients (10.7; interquartile range: 1.78-40.1, vs. 3.79; IQR: 0.37-24.3, respectively; $P = .04$). The findings were published Feb. 5 in the journal *CHEST*®.

The study comprised 89 OSA patients and 38 non-OSA patients who were admitted to a hospital for acute coronary syndromes. The OSA group had a median apnea-hypopnea index (AHI) of 32, while the non-OSA group had a median AHI of 4.8. There was no significant difference between the two groups in gender, age, or cardiovascular risk factors such as hypertension, diabetes mellitus, body mass index, dyslip-

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Fluarix Quadrivalent effective in very young

BY IAN LACY
Frontline Medical News

Fluarix Quadrivalent was highly effective against moderate and severe flu strains in very young children, in a phase 3 observer-blinded randomized trial of 12,018 children, presented at a meeting of the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices.

"Fluarix Quadrivalent, at the 0.5-mL dose in young children 6 to 35 months of age, demonstrated efficacy of 63.2% against moderate to severe influenza and 49.8% against any severity influenza disease," said Leonard Friedland, MD, director of scientific affairs and public health, Vaccines North America, GlaxoSmithKline.

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SOURCE: D-QIV-004.

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Cancer surgery patients helped

// continued from page 1

enough that exercise before surgery should be considered as standard preoperative care.

"Such findings may also [have impacts] on health care costs and on patients' quality of life, and consequently, have important implications for patients, health care professionals and policy makers."

The exercise regimens in the lung cancer studies mostly involved aerobic exercise, such as walking, and breathing exercises to train respiratory muscles, as well as use of an exercise bicycle. The exercises were undertaken in the 1-2 weeks before surgery, with a frequency ranging from three times a week to three times a day.

The authors noted that trials involving a higher frequency of exercise showed a larger effect size, which suggested there was a dose-response relationship.

There was little evidence of benefit in other tumor types. Two studies examined the benefits of preoperative pelvic floor muscle exercises in men undergoing radical prostatectomy and found significant benefits in quality of life, assessed using the International Continence Society Male Short form. However, the authors pointed out that the quality of evidence was very low.

One study investigated the effects of preoperative mouth-opening exercise training in patients undergoing surgery for oral cancer and found enhanced postoperative quality of life in these patients, but the researchers did not report estimates.

These findings may also have impacts "on health-care costs and on patients' quality of life, and consequently, have important implications for patients, health-care professionals, and policy makers," noted Dr. Daniel Steffens and colleagues, in their paper.

For patients undergoing surgery for colon cancer, colorectal liver metastases, and esophageal cancer, there was no benefit of exercise either in postoperative complications or duration of hospital stay. In all these studies, the authors rated the quality of evidence as "very low."

"Despite the evidence suggesting that exercise improves physical and mental health in patients with cancer, there are only a limited number of trials investigating the effect of preoperative exercise on patients' quality of life," the authors wrote. "Therefore, the effect of preoperative exercise on quality of life at short-term and long-term postoperation should be explored in future trials."

No conflicts of interest were declared.

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SOURCE: Steffens D et al. Br J Sports Med. 2018 Feb 1. doi: 10.1136/bjsports-2017-098032.

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House cleaning linked to lung function decline

BY BIANCA NOGRADY
Frontline Medical News

House cleaning is bad for women's lung health, according to a study that has found accelerated decline in lung function among women regularly engaged in cleaning activities.

The longitudinal population-based cohort study, published online Feb. 16 in the American Journal of Respiratory and Critical Care Medicine, looked at the lung health of 6,230 people who were followed for more than 20 years as part of the European Community Respiratory Health Survey.

Analysis based on questionnaires about cleaning practices revealed that women who were responsible for cleaning at home or who worked as professional cleaners showed significantly greater declines in maximum forced vital capacity (FVC) and maximum forced expiratory volume in 1 second (FEV_1), compared with women who said they did not regularly clean.

Female occupational cleaners showed a mean FEV_1 decline of 22.4 mL/year, women who cleaned regularly at home showed a mean decline of 22.1 mL/year, while those who reported no cleaning activities had an 18.5 mL/year decline in FEV_1. For FVC, declines were 15.9 mL/year, 13.1 mL/year, and 8.8 mL/year, respectively. By comparison, the decline in FEV_1 among smokers who smoked at a rate of more than 20 pack-years was 27.2 mL/year, and their decline in FVC was 20.7 mL/year.

"FVC is an outcome of particular interest as survival in asymptomatic adults without a chronic respiratory diagnosis or persistent respiratory symptoms has been shown to be associated with FVC rather than airway obstruction as defined by the lower than normal FEV_1/FVC ratio," wrote Øistein Svanes, a PhD candidate in the department of clinical science at the University of Bergen (Norway) and his coauthors.

However, there was no association between cleaning practices in men – either professional or domestic – and accelerated lung function decline. The authors suggested that the exposures experienced by men who worked as cleaners may have been different from the exposures experienced by women. They also noted that the small numbers of male cleaners meant the study wasn't powered to pick up greater declines in lung function.

The study also showed a significant association between use of cleaning products and decline in lung function. Women who used sprays or other cleaning agents at least once a week showed significantly greater declines in FEV_1 and FVC, compared with women who didn't use cleaning products. Again, this effect was not significant in men.

"One possible mechanism for the accelerated decline in cleaners is the repetitive exposure to low-grade irritative cleaning agents over time, thereby causing persistent changes in the airways," the authors wrote. "Repeated exposure could lead to remodelling of the airways, thereby over time causing an accelerated decline in FVC and FEV_1."

The analysis found no significant increases in the incidence of chronic airway obstruction among regular cleaners, nor among those who used cleaning products. The authors noted that, while previous studies had suggested an increase in chronic obstructive pulmonary disease among occupational cleaners, their study reported relatively few cases of COPD.

While the prevalence of asthma was slightly higher in the two groups of women exposed to regular cleaning (12.3% and 13.7%, versus 9.6%), adjustment for asthma in the analysis did not change the associations. This suggests that the declines in lung function seen in regular cleaners were not mediated by cleaning-related asthma, the researchers noted.

They also noted that the women who reported not engaging in any cleaning may represent a particular socioeconomic group, but adjustment for socioeconomic status did not alter the associations.

The European Community Respiratory Health Survey is supported by the European Union, the European Commission, and the Medical Research Council. No conflicts of interest were reported.

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SOURCE: Svanes Ø et al. Am J Respir Crit Care Med. 2018 Feb 16. doi: 10.1164/rccm.201706-1311OC.

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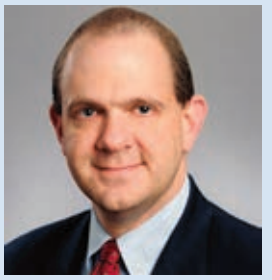

David A. Schulman, MD, FCCP, is Medical Editor in Chief of CHEST Physician.

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CHEST PHYSICIAN (ISSN 1558-6200) is published monthly for the American College of Chest Physicians by Frontline Medical Communications Inc., 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609. Subscription price is $244.00 per year. Phone 973-206-3434, fax 973-206-9378.

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Peak cTn-I levels lower in OSA

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idemia, and smoking.

The cohort was part of the Continuous Positive Airway Pressure (CPAP) in Patients With Acute Coronary Syndrome and Obstructive Sleep Apnea (ISAACC) study, a prior randomized, controlled trial that evaluated the effect of CPAP treatment on new cardiovascular events in patients with an episode of ACS and OSA, reported Alicia Sánchez-de-la-Torre, PhD, of the respiratory department at Hospital Universitari Arnau de Vilanova and Santa Maria in Catalonia, Spain, and her coauthors.

These findings "suggest that patients with higher AHI are significantly more likely to have low cTn-I levels than patients without evidence of OSA, which could imply that patients with elevated AHI, particularly those with severe OSA, may experience less severe myocardial injury," the authors noted.

Respiratory polygraphy was performed in the first 24-72 hours after hospital admission, and patients with an AHI of at least 15 events per hour were considered to have OSA. Those with an AHI less than 15 events per hour were included in the non-OSA group.

The OSA patients were randomized to conservative or CPAP treatment. An obstructive apnea "episode" was defined as a complete cessation of airflow for 10 seconds or longer, and an episode of hypopnea was defined as a reduction in airflow for at least 10 seconds associated with a greater than 4% decrease in arterial oxygen saturation.

Blood samples were collected from patients every 6 hours until two consecutive cTn-I measurements showed a decrease, with the highest measurement considered the peak cTn-I value.

Peak cTn-I value was significantly higher in non-OSA patients than in OSA patients. Median infarct size, measured by calculating the area under the cTn-I curve, was significantly different between the two groups (451 for non-OSA patients vs. 143 in OSA patients; $P = .049$), wrote Dr. Sánchez-de-la-Torre and her colleagues.

As cTn-I levels decreased, there was a trend toward increased OSA severity ($P = .058$). In the multivariable linear regression model used to assess OSA severity, patients with severe OSA had 61% lower cTn-I levels than non-OSA patients, the authors noted.

"The effects of chronic hypoxia in individual organ systems are not well understood. While chronic sustained hypoxia as seen with COPD may lead to pulmonary hypertension, chronic intermittent hypoxia (CIH) as seen predominantly in sleep apnea has been attributed to causing widespread effects ranging from systemic hypertension to metabolic dysfunction and systemic inflammation," noted Krishna Sundar, MD, FCCP. "Despite these associations, an increased risk of major cardiovascular events from untreated OSA is yet to be definitively established."

"The effects of chronic hypoxia in individual organ systems are not well understood," said Dr. Krishna Sundar.

In this article, a protective effect from OSA on myocardial ischemic events is demonstrated in a group of 127 consecutively admitted patients with acute coronary syndrome (ACS). While it is interesting that a high proportion of those admitted for ACS had OSA, there were no significant differences in the age, sex, BMI, usage of antihypertensive or antiplatelet agents, presence of hypertension, DM, dyslipidemia or smoking status between those with and without OSA. "OSA appeared to confer a protective effect on the size of myocardial injury with those having higher AHI values demonstrating lower peak cardiac troponin values," said Dr. Sundar, who is an associate clinical professor of pulmonary, critical care and sleep medicine at the University of Utah.

"An effect of age (mean age in this study being 64 years) and BMI (mean being 27) on the occurrence of preconditioning effects of OSA is not excluded given deleterious effects of untreated OSA on infarct size in other studies on obese or younger patients with ACS. Further understanding of molecular effects of chronic hypoxia exposure (high altitude, chronic lung disease, OSA) is required before the complex and often contradictory effects of chronic hypoxia can be affirmed as being protective or deleterious," added Dr. Sundar, who is also medical director of the Sleep-Wake Center at the University of Utah and a member of *CHEST Physician*'s editorial advisory board.

According to the study's authors, their findings "suggest that patients with higher AHI are significantly more likely to have low cTn-I levels than patients without evidence of OSA, which could imply that patients with elevated AHI, particularly those with severe OSA, may experience less severe myocardial injury."

Limitations of the study include exclusion of patients with severe ACS, exclusion of sleepy subjects, and assessment of myocardial injury using cTn-I as a biomarker, without further data to determine infarct size.

"The possible role of OSA in cardioprotection should be explored in future studies," the authors concluded.

The authors disclosed relationships with ResMed, Spanish Ministry of Health, Spanish Respiratory Society, Catalonian Cardiology Society, and ALLER. No other disclosures were reported.

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SOURCE: Chest. 2018 Feb 5;153[2]:329-38. doi: 10.1016/j.chest.2017.06.046.

Results demonstrate 'paradigm shift' in OSA research

Although this study cannot definitively establish a clinically meaningful protective effect, it does provide important "preliminary evidence supporting the concept of OSA-induced cardioprotection" and challenges existing research, according to an editorial by Doron Aronson, MD, of the department of cardiology at Rambam Medical Center, Haifa, Israel, and coauthors (CHEST. 2018 Feb 153[2]:295-7. doi: 10.1016/j.chest.2017.07.036).

The results should be interpreted with caution, especially since accurate assessment of infarct size poses a challenge, they wrote.

"Myocardial infarct size is highly variable and is influenced by the duration of coronary occlusion, ST-segment elevation or non–ST elevation myocardial infarction, infarct location, residual antegrade infarct-related artery flow, collateral flow, the presence of non–culprit vessel coronary artery disease and myocardial metabolic demand," they wrote. "Without accounting for these variables in a small study, results may be affected by variation in the characteristics of the patients."

Though further study is needed, the findings may have "profound clinical implications regarding our therapeutic approach to patients with sleep apnea" if confirmed, the authors concluded.

OSA Endotypes and Phenotypes: Toward Personalized OSA Care

BY ROBERT L. OWENS, MD; NAOMI DEACON, PHD; AND ATUL MALHOTRA, MD, FCCP

Dr. Owens is Assistant Clinical Professor of Medicine; Dr. Deacon is a Post-Doctoral Research Scholar; and Dr. Malhotra is Kenneth M. Moser Professor of Medicine and Chief, Division of Pulmonary, Critical Care and Sleep Medicine, University of California San Diego.

Obstructive sleep apnea (OSA) contributes a major health burden to society due to its high prevalence and substantial neurocognitive and cardiovascular consequences. Estimates suggest that at least 10% of adults in North America are afflicted with OSA, making it probably the most common respiratory disease in the developed world (Peppard et al. *Am J Epidemiol.* 2013;177[9]:1006). Nasal CPAP is a highly efficacious therapy that has been shown to improve neurocognitive and cardiovascular outcomes. However, CPAP is not always well tolerated. Alternative therapies, such as oral appliances and upper airway surgery, have highly variable efficacy, and evidence of important clinical benefits are uncertain. Therefore, efforts are ongoing to determine optimal alternative strategies for therapy.

In order to treat any condition optimally, one needs to be able to predict who is at highest risk of developing the condition, then to assess the consequences if left untreated, and finally to be able to predict response to various treatment options. Currently, the OSA field is still in its early stages of our understanding. Clinically, we are often faced with patients who have varying presentations and manifestations, but, for reasons that are unclear. For instance, two individuals with the same body mass index may have very different clinical manifestations, one with severe OSA and one without any OSA. Similarly, two individuals with an apnea hypopnea index of 40 events per hour (ie, severe OSA) may have very different symptoms attributable to OSA, eg, one could be asymptomatic and the other could be debilitated from sleepiness. We and others have been making efforts to determine why these phenomenon occur. At present, the techniques to define mechanisms underlying OSA are labor-intensive, requiring one or two overnight experiments to gather meaningful data. Although we are gathering new insights based on these techniques, efforts are ongoing to simplify these approaches and to make assessment of pathophysiologic characteristics more accessible to the clinician (Orr et al. *Am J Respir Crit Care Med.* 2017 Nov 30. doi: 10.1164/rccm.201707-1357LE. [Epub ahead of print]).

We ultimately believe that a thorough analysis of a sleep recording combined with demographic data and other readily available clinical data (perhaps plasma biomarkers) may yield sufficient information for us to know why OSA is occurring and what interventions might be helpful for an individual patient. Currently, our use of the polysomnogram to derive only an apnea hypopnea index does not take full advantage of the available data. An apnea hypopnea index can be readily obtained from home sleep testing and does not truly provide much insight into why a given individual has OSA, what symptoms are attributable to OSA, and what interventions might be considered for the afflicted individual. By analogy, if the only useful data derived from an ECG were a heart rate, the test would rapidly become obsolete. Along these lines, if the only role for the sleep clinician was to prescribe CPAP to everyone with an AHI greater than 5/h, there would be little need or interest in specialized training. In contrast, we suggest that rich insights regarding pathophysiology and mechanisms should be gathered and may influence clinical management of patients afflicted with OSA. Thus, we encourage more thorough analyses of available data to maximize information gleaned and, ultimately, to optimize clinical outcomes.

Recent studies suggest that sleep apnea occurs for varying reasons, a concept that is now thought to be clinically important (Jordan et al. *Lancet.* 2014;383[9918]:736). We draw a crucial distinction between endotypes (mechanisms underlying disease) and phenotypes (clinical expression of disease). Important endotypes include compromised upper airway anatomy, dysfunction in pharyngeal dilator muscles, unstable ventilatory control (high loop gain), and low arousal threshold (wake up easily), among others. Important phenotypes of sleep apnea are emerging and still evolving to include minimally symptomatic OSA, OSA with daytime sleepiness, and OSA with major cardiometabolic risk, among others. Several important concepts have emerged regarding different OSA endotypes and phenotypes:

1 The mechanism underlying OSA may predict potential response to therapeutic interventions. For instance, the endotype of OSA with unstable ventilatory control (high loop gain) may respond to agents such as oxygen and acetazolamide, which serve to stabilize control of breathing. In patients with anatomical compromise at the level of the velopharynx, uvulopalatopharyngoplasty may be an effective intervention. For patients with multiple pathophysiologic abnormalities, combination therapy may be required to alleviate OSA (Edwards et al. *Sleep.* 2016;9[11]:1973).

2 Given that OSA has many underlying etiologies, efforts are underway to determine whether individuals with different risk factors for OSA develop their disease based on varying mechanisms. As an example, people with posttraumatic stress disorder (PTSD) may be at increased risk of OSA perhaps on the basis of a low threshold for arousal (Orr et al. *JCSM.* 2017, 13[1]: 57-63). Another example would be patients with neuromuscular disease who may be at risk of OSA primarily based on impaired pharyngeal dilator muscle function.

3 A new concept is emerging whereby endotypes of OSA may actually predict differing OSA phenotypes. In theory, loop gain-driven OSA may have different consequences from OSA driven by compromise of pharyngeal anatomy. To this point, data suggest that OSA in the elderly may not have as many consequences as OSA in younger people matched on severity of illness. OSA in the elderly has lower loop gain than OSA in younger people and is associated with less negative intrathoracic pressure at the time of arousal as compared with younger individuals with OSA (Kobayashi et al. *Chest.* 2010; 137[6]:1310). As such, the endotype of OSA in the elderly may explain why the clinical consequences are fewer than in the younger OSA counterparts.

4 The mechanism underlying OSA may be important in determining response to clinical interventions, such as nasal CPAP. Patients with a low arousal threshold may be prone to insomnia when placed on CPAP and could theoretically be poorly tolerant of therapy based on disrupted sleep architecture. Such patients may benefit from non-myorelaxant hypnotic therapy to consolidate sleep and improve CPAP adherence. In addition, patients with high loop gain (unstable ventilatory control) may be prone to develop central apneas when placed on CPAP therapy (Stanchina et al. *Ann Am Thorac Soc.* 2015;12[9]:1351). These patients may benefit from newer technologies, eg, auto or adaptive servo ventilation - ASV. High loop gain has also been shown to predict failure of upper airway surgery as a treatment for OSA by several groups (Li et al. *JCSM.* 2017;13[9]:1029). Such patients should, perhaps, undergo nonsurgical therapies for OSA.

We emphasize that some of the points being made are somewhat speculative and, thus, encourage further basic and clinical research to test our assumptions. Robust, multicenter clinical trials assessing hard outcomes will ultimately be required to change the current standard of care. Nonetheless, we believe that a more thorough understanding of OSA pathogenesis can help guide clinical care today and will be critical to the optimal treatment of afflicted individuals tomorrow.

CPAP adherence linked to reduced readmissions

BY ELI ZIMMERMAN
Frontline Medical News

Hospitalized patients with obstructive sleep apnea (OSA) who were nonadherent to continuous positive airway pressure (CPAP) treatment were more than three times as likely to be readmitted for complications, according to a study.

Since preventable causes of readmission like congestive heart failure, obstructive lung disease, and diabetes are connected to OSA, boosting adherence rates to sleep apnea treatment could be an effective way to mitigate these risks.

"Nonadherence to CPAP has been associated with increased chronic obstructive pulmonary disease (COPD) exacerbations, worsened insulin resistance, psychiatric illnesses, and

Continued on following page

Cost-effectiveness of CPAP adherence

The comorbidities associated with obstructive sleep apnea (OSA), such as heart failure, coronary artery disease, diabetes, and stroke, can be detrimental to patients' care and commonly lead to hospitalization. Not only are these diseases interfering with successful treatment, but financial penalties linked to 30-day readmissions have economic implications for hospitals as well. Increasing CPAP adherence, therefore, may be a low-cost tool to improve hospital outcomes. Dr. Truong and her colleagues find compelling data showing the association of CPAP adherence and reduced 30-day readmissions. However, more work is needed before we can fully back the idea that CPAP adherence will prevent readmissions. While many studies have shown associations between OSA and cardiovascular events, there are no large, randomized trials that show the cardiovascular benefit of CPAP. The current theory is that patients who are adherent to CPAP are more likely to be healthier individuals, which makes them less likely to exhibit the comorbidities that would cause readmissions. A large randomized trial is the next logical step, and with OSA costs estimated at $2,000 annually per patient, it is a step worth pursuing.

Lucas M. Donovan, MD, is a pulmonologist at the University of Washington, Seattle. Martha E. Billings, MD, is an assistant professor in the division of pulmonary and critical care medicine at the University of Washington, Seattle. They reported no conflicts of interest.

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lower urinary tract symptoms," wrote Kimberly K. Truong, MD, MPH, an internist at the University of California, Irvine, and her fellow investigators in a study published in the Journal of Clinical Sleep Medicine. That OSA is not only common and linked with other help problems but also can be treated readily with CPAP "makes it an important clinical and public health disease to target."

Investigators gathered data for 345 hospitalized

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patients with OSA who were admitted to the VA Long Beach (Calif.) Healthcare System between January 2007 and December 2015.

Both the adherent and nonadherent groups were mostly white males. The 183 adherent patients were, on average, slightly older than the patients in the nonadherent group (66.3 vs. 62.3 years), while the nonadherent group had a larger proportion of African Americans (19.1%) than did the adherent group (10.4%).

"Nonadherence to CPAP has been associated with increased chronic obstructive pulmonary disease (COPD) exacerbations, worsened insulin resistance, psychiatric illnesses, and lower urinary tract symptoms," wrote Kimberly K. Truong, MD, MPH, and colleagues.

In an analysis of both groups, 28% of nonadherent patients were readmitted within 30 days of discharge, compared with 10.2% of those in the adherent group (*P* less than .001). Readmission rates were significantly higher for nonadherent patients brought in for all causes (adjusted odds ratio, 3.52; *P* less than .001), as were their rates of cardiovascular-related readmission (AOR, 2.31; *P* = .02).

The cardiovascular-related readmissions were most often caused by atrial fibrillation (29%), myocardial ischemia (22.5%), and congestive heart failure (19.3%) in the group who were not using CPAP. In this same group, urologic problems (10.7%), infections (8.0%), and psychiatric issues (5.3%) were the most common causes for hospital readmissions.

"Those with OSA and COPD are considered to have overlap syndrome and, without CPAP therapy, are at higher risk for COPD exacerbation requiring hospitalization, pulmonary hypertension, and mortality," according to the investigators.

Investigators were surprised to find that the rate of pulmonary-related readmissions was not higher among nonadherent patients, considering the shared characteristics of OSA and COPD.

While nonadherent patients had an adjusted rate of pulmonary-related readmissions of 3.66, the difference between nonadherent and adherent patients was not significant.

"Those with OSA and COPD are considered to have overlap syndrome and, without CPAP therapy, are at higher risk for COPD exacerbation requiring hospitalization, pulmonary hypertension, and mortality," according to Dr. Truong and her colleagues. "However, the number of patients with pulmonary readmissions was very small, and analysis did not reach statistical or clinical significance."

Given the single-center nature of the study, these findings have limited generalizability. The study may also have been underpowered to uncover certain differences between the two groups because of the small population size.

The investigators reported no relevant financial disclosures.

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SOURCE: K. Truong et al. J Clin Sleep Med. 2018;14(2):183-9.

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OSA patients report sleeping better with dronabinol

BY BIANCA NOGRADY
Frontline Medical News

Obstructive sleep apnea patients reported sleeping better and experienced less apnea and hypopnea events after taking dronabinol, in a new study.

A paper published in the January edition of Sleep presents data from a phase 2, blinded, randomized controlled trial of the nonselective cannabinoid 1 and cannabinoid 2 receptor agonist, dronabinol, in 73 adults with moderate or severe obstructive sleep apnea (OSA). No approved drug treatments for OSA exist, and this study provides results "from the largest and longest randomized controlled trial to date of any putative drug treatment for OSA," the researchers wrote.

Patients were randomized to 2.5 mg dronabinol or 10 mg dronabinol daily for up to 6 weeks, or placebo. At the end of treatment, researchers saw significant increases in the apnea-hypopnea index among the patients on placebo, while those who received dronabinol showed decreases in the number of apnea and hypopnea events per hour. Patients given the 2.5-mg dose of dronabinol had a mean decrease of 10.7 events per hour, and those on the 10-mg dose had a mean decrease of 12.9 events per hour compared with placebo.

The difference between the placebo and treatment arms was significant for both dosages, and the apnea-hypopnea index decreases were similar between the two dosages of dronabinol.

Questioning the apnea-hypopnea index

This study has found a small overall effect on the apnea-hypopnea index with treatment, but a strong beneficial effect on subjective sleepiness. In addition, participants who received the higher dose of the drug showed significant satisfaction with their therapy. It is therefore intriguing that there was no impact on objective wakefulness or sleep architecture with this treatment.

This suggests that perhaps sleepiness and subjective well-being may be improved without necessarily seeing major improvements in the apnea-hypopnea index, which calls into question our use of this index as a primary endpoint.

Sigrid C. Veasey, MD, is with the Center for Sleep and Circadian Neurobiology at the Perelman School of Medicine, University of Pennsylvania, Philadelphia. Her comments were taken from an accompanying editorial (Sleep. 2018 Jan 1. doi: 10.1093/sleep/zsy014). She reported no conflicts of interest.

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These effects were largely due to reductions in apnea events; the largest reduction was seen in the REM apnea index in patients treated with the 10-mg dose of dronabinol. However, there were few effects on the expression of hypopneas, except in the higher-dose group.

After adjustment for age, race, ethnicity, and baseline apnea-hypopnea index, the increases seen in the placebo group were no longer significant, but the decreases from baseline seen in the treatment arms were greater.

This study provides results "from the largest and longest randomized controlled trial to date of any putative drug treatment for OSA," according to David W. Carley, PhD, of the University of Illinois at Chicago, and colleagues.

Dronabinol treatment was also associated with significant decreases, compared with placebo, in non-REM apnea-hypopnea index and REM apnea-hypopnea index.

Patients' self-reported daytime sleepiness, measured by the Epworth Sleepiness Scale, remained similar compared with baseline in those who received placebo and the

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Continued from previous page

2.5-mg/day dose of dronabinol, but decreased significantly by a mean of –2.3 points compared with placebo in those on the higher dose of dronabinol.

There were no significant changes from baseline in objective sleepiness, as measured by the maintenance of wakefulness test, in any of the study groups. Researchers also saw no significant changes in sleep architecture, oxygenation, or the duration of supine sleep in any of the study groups, although the patients on the higher dose of dronabinol showed a slight increase in REM sleep and those on placebo showed a slight decrease.

There were no significant changes from baseline in objective sleepiness, as measured by the maintenance of wakefulness test, in any of the study groups.

Younger patients and those with a greater preponderance of REM-related apnea/hypopnea, and shorter average event duration were both more likely to respond to treatment, but apart from these factors there were no other influences on likelihood of patients responding to dronabinol.

David W. Carley, PhD, of the University of Illinois at Chicago, and his coauthors noted that there was a great need for pharmacological treatments for obstructive sleep apnea because positive airway pressure – while effective – has poor long-term adherence rates.

"Based on a series of animal investigations, we proposed that drugs which dampen afferent vagal feedback to the medulla may be effective in stabilizing respiratory pattern generation and increasing activation of upper airway dilating muscles during sleep," they wrote.

One patient experienced diarrhea and vomiting that required admission to hospital, and which was judged as possibly related to the study medication. There were six other withdrawals due to adverse events including dizziness and vision changes, vertigo, ECG arrhythmias, and headache with dizziness and vomiting. Overall, nearly 90% of patients reported at least one adverse event, but the rates did not differ significantly between the treatment and placebo arms.

The researchers noted that significantly higher satisfaction scores were seen among patients receiving the higher dose of dronabinol.

"All of these observations argue that dronabinol, at doses from 2.5 to 10 mg/day, is safe for use by medically stable patients with moderate or severe OSA," the authors wrote. "Participants also tolerated and adhered well to daily self-administration of dronabinol."

The National Institutes of Health; National Heart, Lung, and Blood Institute; and National Center for Advancing Translational Sciences funded the study. One author declared grants from the National Institutes of Health for the study, and patents related to treatment of sleep-related breathing disorders by cannabinoid drugs. He also holds stock in RespireRx Pharmaceuticals, which holds an exclusive license to these and other related patents.

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SOURCE: Carley D, et al. Sleep. 2018 Jan 1. doi: 10.1093/sleep/zsx184.

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Adenotonsillectomy reduced hypertension in OSA subgroup

BY KATIE WAGNER LENNON
Frontline Medical News

Hypertensive children with obstructive sleep apnea (OSA) who underwent adenotonsillectomy experienced significant improvements in their blood pressure after surgery, according to a retrospective analysis.

This is one of the few studies to have ever examined whether adenotonsillectomy for children with OSA had any effects on blood pressure and was based on "one of the largest cohorts for evaluating postoperative BP changes in nonobese children with OSA," noted Cho-Hsueh Lee, MD, and colleagues. The report was published in JAMA Otolaryngology–Head & Neck Surgery. Among the previous studies that evaluated BP in children with OSA before and after having this surgery, the results varied, they added.

"Our subgroup analysis results revealed that hypertensive children with OSA had significant improvements in all BP measures after surgery," wrote Dr. Cho-Hsueh Lee and colleagues.

"Our subgroup analysis results revealed that hypertensive children with OSA had significant improvements in all BP measures after surgery," wrote Dr. Lee, of the department of otolaryngology at National Taiwan University Hospital in Taipei, and coauthors. "These findings highlight the need to screen children with OSA to determine their hypertensive status and appropriately treat these children to ease their OSA symptoms and potentially prevent future adverse cardiovascular outcomes."

The researchers analyzed the medical records of 240 nonobese children with clinical symptoms and polysomnography-confirmed OSA (having an apnea-hypopnea index of greater than 1) who underwent adenotonsillectomy. Prior to surgery, 169 patients (70.4%) of the patients were classified as nonhypertensive, while 71 (29.6%) were classified as hypertensive. The children had a mean age of 7.3 years, and 160 were males.

Patients participated in full-night polysomnography (PSG) before surgery and at 3-6 months after adenotonsillectomy in the National Taiwan University Hospital Sleep Center. Apnea episodes were defined as a 90% decrease in airflow for two consecutive breaths. Sleep center staff measured the study participants' systolic and diastolic BP in a sleep center using an electronic sphygmomanometer, in the evening, prior to the PSG study, and in the morning. Pediatric hypertension was based on the nocturnal BP measurement and was defined as having mean systolic and diastolic BP greater or equal to the 95th percentile for age, sex, and height.

"Postoperatively, hypertensive children had a significant decrease in all BP measures, including nocturnal and morning [systolic] BP. ... A total of 47 hypertensive patients (66.2%) became nonhypertensive after surgery," the researchers said.

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"Postoperatively, hypertensive children had a significant decrease in all BP measures, including nocturnal and morning [systolic] BP. ... A total of 47 hypertensive patients (66.2%) became nonhypertensive after surgery," the researchers said.

For patients who were hypertensive before surgery, the average nocturnal (before PSG) preop systolic BP was 114.3 mm Hg, versus 107.5 mm Hg after surgery. The mean nocturnal diastolic BP for this same group of patients decreased to 65.1 mm Hg from 74.3 mm Hg. Similarly, the average morning (after PSG) systolic BP and diastolic BP were 106.0 mm Hg and 64.4 mm Hg after these patients underwent adenotonsillectomy, compared with 111.8 mm Hg and 71.7 mm Hg prior to surgery, respectively.

The adenotonsillectomy didn't improve all patients' BP. For some who were nonhypertensive before surgery, blood pressure increased, with 36 (21.3%) of this group having become hypersensitive after surgery, the researchers acknowledged.

Overall, the cohort experienced significant improvements in several PSG measures, including the average apnea-hypopnea index, which decreased from 12.1 events per hour to 1.7. The total arousal index also declined, going from 6.1 events per hour to 4.2. In addition, the mean oxygen saturation improved from 96.8% to 97.7%.

The investigators described several limitations of the study, including their inability to collect patients' arterial stiffness, carotid intima thickness, and other cardiovascular measures beyond BP.

They recommended a follow-up study. "Although we observed improvements in BP measures within 6 months after surgery for hypertensive children with OSA, the long-term effects of surgery on BP remain uncertain," they explained.

The study was supported by grants from the Ministry of Science and Technology, Republic of China (Taiwan). The researchers disclosed no potential conflicts of interest.

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SOURCE: Lee, C-H et al. JAMA Otolaryngol Head Neck Surg. 2018 Feb 15. doi: 10.1001/jamaoto.2017.3127.

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: This pediatric study from Taiwan is important because it shows that hypertension is a significant issue in nonobese children and can be modulated by treatment for OSA. The only concern I have is that blood pressure normative reference data were adopted to Taiwanese children from the National High Blood Pressure Education Program working group in the United States. Our sleep clinic at Helen DeVos Children's Hospital often receives referrals from Pediatric Cardiology and Pediatric Nephrology for sleep studies for hypertensive patients. Hopefully, because of this publication, primary care providers will also consider OSA in their work-up for pediatric hypertension!

Radiation exposure in MICU may exceed recommended limit

BY ANDREW D. BOWSER
Frontline Medical News

FROM THE JOURNAL *CHEST*® ▪ Patients admitted to medical intensive care units may be exposed to doses of radiation that are substantial and exceed federal annual occupational limits, according to results of a recent observational study.

These "substantial" radiation doses in some patients suggest that efforts are warranted to "justify, restrict and optimize" the use of radiological resources when possible, said Sudhir Krishnan, MD, of the Cleveland Clinic, and his coauthors.

"Although we were unable to assess or predict the potential long-term adverse effects of radiation exposure, judicious use of radiological resources is recommended," Dr. Krishnan and his colleagues wrote in the journal *CHEST*®.

The retrospective, observational study included 4,155 adult admissions to a medical intensive care unit (MICU) at an academic medical center in 2013. Investigators calculated the cumulative effective dose (CED) of radiation based on ionizing radiological studies for each patient.

With a median length of stay of just 6.4 days, a total of 131 admissions (3%) accrued a CED of radiation of at least 50 millisieverts (mSv), the annual limit recommended by the National Commission on Radiation Protection, and 47 of those patients (1%) accrued a CED of radiation of at least 100 mSv, the 5-year cumulative exposure limit, the authors reported.

These findings suggest that "MICU patients could be subjected to radiation doses in a matter of days that are equivalent to or more than [the] CED observed in patients with chronic diseases and patients with trauma," they wrote.

As hypothesized, patients with higher severity of illness scores (APACHE III scores) received a higher CED of radiation, according to the report. Using a multivariable linear regression model, investigators found that higher CED was predicted by higher APACHE III scores, sepsis, longer MICU stay, and gastrointestinal disorders and bleeding.

CT scans were the most common source of radiation exposure in patients who exceeded a 50 mSv of radiation, accounting for 49% of the total accrued dose, with interventional radiology accounting for 38%.

Despite concerns about "the statistical risk of latent radiogenic cancer," radiologic studies performed in the critically ill have the potential to reduce morbidity and mortality, the authors acknowledged. "This understandably shifts the risk-benefit ratio towards radiation exposure. However, complacency in this regard cannot be entirely justified," they wrote.

Of the patients in the study who were exposed to a CED of at least 50 mSv, 81% survived the hospital admission and could be subjected to even more radiation as a part of ongoing medical care, they noted.

"Robust tools for monitoring CED prospectively per episode of clinical care, counseling patients exposed to high doses of radiation, and prospective studies exploring radiogenic risk associated with medical radiation are urgently required," the authors said.

The investigators reported no significant conflicts of interest.

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SOURCE: Krishnan S et al. Chest. 2018 Feb 4. doi: 10.1016/j.chest.2018.01.019.

VIEW ON THE NEWS

Nirmal S. Sharma, MD, comments: This is a very valid study. I think radiation exposure in the ICU is too high. Previous studies have shown that doing imaging on demand has had similar outcomes to doing it daily. (Currently, across the country, chest x-rays are done daily for most patients in the ICU, who have a respiratory problem.) We tried using this model at the University of Alabama at Birmingham, but some physicians were not comfortable with it and had to revert to previous practices. We would need future studies to find out if the radiation exposures in survivors from the ICU results in increased incidence of malignancies at a later date.

FDA approves angiotensin II for shock patients

BY IAN LACY
Frontline Medical News

Angiotensin II has been approved for use in intravenous infusions to increase blood pressure in adults with septic or other distributive shock, the Food and Drug Administration announced.

Shock-related drops in blood pressure can restrict blood flow to vital organs and can result in organ failure and death. "There is a need for treatment options for critically ill hypotensive patients who do not adequately respond to available therapies," Norman Stockbridge, MD, PhD, director of the division of cardiovascular and renal products in the FDA's Center for Drug Evaluation and Research, said in a written statement.

The effectiveness of angiotensin II for treating critically low blood pressure was confirmed in a clinical trial of 321 patients who were in shock. A significant number of patients responded to angiotensin II treatment, compared with those given placebo. In combination with conventional treatments, angiotensin II increased blood pressure safely and effectively, according to the FDA statement.

The application for angiontensin II was received under Priority Review, which asks the FDA to take action on an application within 6 months if the agency determines that an approved drug would improve the safety and effectiveness of treating a serious medical condition.

The angiotensin II injections, which would be marketed as Giapreza by La Jolla Pharmaceutical Company if approved, can cause serious blood clots.

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Combo therapy does not improve outcomes for *A. baumannii*

BY HEIDI SPLETE
Frontline Medical News

Adding meropenem to colistin had no effect on clinical success in cases of severe *Acinetobacter baumannii* infections, based on data from 406 patients.

In a study published online in The Lancet Infectious Diseases, Mical Paul, MD, of Rambam Health Care Campus, Haifa, Israel, and colleagues randomized 198 patients to colistin alone and 208 to colistin plus meropenem (Lancet Infect Dis. 2018 Feb 15. doi: 10.1016/S1473-3099[18]30099-9).

The demographics were similar between the groups and approximately 77% of patients in each group were infected with *A. baumannii*.

The primary outcome was defined as clinical success 14 days after randomization; 79% (156) of the colistin-only patients and 73% (152) of the combination patients did not meet the criteria, the researchers said. In addition, no significant difference between the groups was noted in all-cause mortality at 14 days or 28 days, or for any other secondary outcomes including fever and time spent in the ICU.

The results highlight "the necessity of assessing combination therapy in randomized trials before adopting it into clinical use," the researchers said.

The study was not designed to examine the effect of the two types of therapy on bacteria other than *A. baumannii*, the researchers noted. However, based on the findings, "we recommend against the routine use of carbapenems for the treatment of carbapenem-resistant *A. baumannii* infections," they said.

The study was supported by EU AIDA grant Health-F3-2011-278348. Dr. Paul had no financial conflicts to disclose.

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SOURCE: Paul M et al. Lancet Infect Dis. 2018 Feb 15. doi: 10.1016/S1473-3099(18)30099-9.

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Perfusion-only scan rules out PE in pregnancy

BY ANDREW D. BOWSER
Frontline Medical News

FROM THE JOURNAL *CHEST*® ▪ For pregnant women with suspected pulmonary embolism (PE), evaluation with low-dose perfusion scintigraphy may be preferable to computed tomographic pulmonary angiography (CTPA), according to authors of a recent retrospective study.

Pulmonary embolism causes 9% of maternal deaths in the United States, according to the authors of the study, which was published online in the journal *CHEST*®. While it's clear that perfusion scans yield lower radiation exposure than CTPA, to date, there has been only limited study of its diagnostic performance in women with suspected PE.

The negative predictive value was a particularly important endpoint to evaluate because pulmonary embolism is rare among pregnant women and most perfusion-only imaging is negative, according to the investigators.

The new study is believed to be the largest to date of perfusion-only imaging in this setting, according to first author Jean-Ju Sheen, MD, of the department of obstetrics and gynecology at Columbia University Medical Center, New York, and her coauthors.

The low-dose perfusion scan offered comparable diagnostic efficacy while potentially limiting radiation exposure, according to the authors of this single-center, retrosepctive cohort study.

The study included pregnant women (mean age, 27.3 years) who underwent imaging for pulmonary embolism at Montefiore Medical Center, New York, between 2008 and 2013. A total of 225 women underwent perfusion-only scans, while 97 underwent CTPA.

Chest pain and dyspnea were the most common symptoms for patients in both groups: 136 of the patients (60.4%) in the low-dose perfusion group reported chest pain versus 40 patients (41.2%) in the CTPA group. Additionally, approximately half of the patients in both groups had dyspnea.

Tachycardia was found in 43 of patients (44.3%) who underwent CTPA, compared with 77 of the patients (34.2%) who underwent the diagnostic test involving less radiation exposure.

Imaging was negative for PE in 198 of the patients (88.0%) who were scanned with low-dose perfusion, while 84 of patients (86.6%) who had CTPAs were negative for PE. For both groups of patients, the percentage who had indeterminate imaging was 9.3%. Only one study participant had a deep vein thrombosis at the time she presented with PE symptoms.

The primary end point of the study, negative predictive value, was 100% for the perfusion-only group and 97.5% for CTPA, according to the report. It was determined by a diagnosis of venous thromboembolism within 90 days of evaluation.

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Those "indistinguishable" negative predictive values suggest that low-dose perfusion scintigraphy performs comparably to CTPA, making it an appropriate first diagnostic modality for pregnant women who are suspected of having pulmonary embolism, wrote Dr. Sheen and her colleagues.

The negative predictive value was a particularly important endpoint to evaluate because pulmonary embolism is rare among pregnant women and most perfusion-only imaging is negative, the authors stated.

Of the women in the study, 252 (89%) of those who tested negative for PE – either by a low-dose perfusion scan or a CTPA – returned to the medical center for follow-up 90 days later.

Thromboembolic events occurred in two of the women who previously had a negative CTPA, but none occurred in patients who had been tested for PE with low-dose perfusion scan. The two thromboembolic events were detected in women who were no longer pregnant.

Ten patients in the study (3.1%) were treated for pulmonary embolism, the authors reported. The PE diagnoses were based on four positive low-dose perfusion scans and six positive CTPAs "in conjunction with clinical suspicion." These patients' most common symptoms were chest pain and dyspnea.

Only one of these patients had recently been diagnosed with a deep vein thrombosis.

When perfusion defects are found, they should be interpreted cautiously, particularly in asthmatic patients, the researchers noted.

"Segmental perfusion defects secondary to abnormal ventilation cannot be distinguished from PE without a ventilation scan," added the investigtors.

Three of the patients diagnosed with a PE had asthma. In a subanalysis of the 77 patients with asthma who participated in this study, the negative predictive values were 100% for both those who received a low-dose perfusion scan and those who received a CTPA. For patients in this subgroup, the negative rates of PE from low-dose perfusion scan and CTPA were 74.1% and 87.1%, respectively.

"Maternal-fetal radiation exposure should be of utmost importance when considering the choice of diagnostic test," the authors wrote. "When available, [a low-dose perfusion scan] is a reasonable first choice modality for suspected pulmonary embolism in pregnant women with a negative chest radiograph."

One study coauthor is on an advisory panel for Jubilant DraxImage, and another has a spouse who is a board member of Kyron Pharma Consulting.

The remaining authors, including Dr. Sheen, reported no conflicts of interest.

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SOURCE: Sheen JJ et al. Chest. 2018 Feb. doi: 10.1016/j.chest.2017.08.005.

VIEW ON THE NEWS

Nirmal S. Sharma, MD, comments: During pregnancy, all radiation is bad radiation, but when it was really needed, we did use this low-radiation perfusion scan quite a bit at my past institution. This article definitely shines light on the utility/validity of this technique because most centers still use a computed tomographic pulmonary angiography study in pregnant females (with shielding methods) if suspicion of pulmonary embolism is high. The downside to low-dose perfusion scintigraphy is that it cannot be used in patients with grossly abnormal chest x-rays.

If you are doing a low-dose perfusion scan alone, without ventilation studies, in subjects who have ventilation issues caused by severe parenchymal disease or an obstructive lung disease, such as asthma, interpretation becomes an issue. Such patients may have segmental and subsegmental perfusion defects caused by loss of ventilation.

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Twitter content analysis reveals clinical opportunity

BY CHHAVI JAIN
Frontline Medical News

Social media communication around lung cancer is focused primarily on cancer treatment and use of pharmaceutical and research interventions, followed closely by awareness, prevention, and risk topics, according to an analysis of Twitter conversation over a 10-day period.

Although awareness and risk prevention tweets were likely to contain cues toward action, "messages focused on treatment, end of life ... were significantly less likely to integrate cues for personal activity," the investigators wrote. The report was

"[These] findings suggest an opportunity to increase cues to action across all phases of the communication continuum," wrote Dr. Jeannette Sutton and her colleagues.

published in Journal of the American College of Radiology.

"Such findings suggest an opportunity to increase cues to action across all phases of the communication continuum," wrote Jeannette Sutton, PhD, of the University of Kentucky, Lexington, and her colleagues.

The investigators collected 1.3 million unique Twitter messages between Sept. 30 and Oct. 9, 2016, that contained at least one of six keywords commonly used to describe cancer: cancer, chemo, tumor, malignant, biopsy, and metastasis. They then drew a random, proportional stratified sample of 3,000 messages (12.5%) for manual coding from the 23,926 messages posted that included keywords related to lung cancer. Tweets were examined by user type (individuals, media, and organizations) to identify content and structural message features.

Message content was most frequently related to treatment (32.1%), followed by awareness (22.9%), end of life (15.5%), prevention and risk information (13.3%), active cancer-unknown phase (7.6%), diagnosis (6.1%), early detection (2.7%), and survivorship (1%), Dr. Sutton and her colleagues reported.

"The large volume of messages containing content about pharmaceuticals suggests that Twitter is also a forum for sharing information and discussing emerging treatments. Importantly, treatment messages were shared primarily by individuals, suggesting that this online user community jointly includes members of the public as well as medical practitioners and companies who have an awareness of emerging treatment approaches, suggesting an opportunity for online engagement between these various groups (e.g., Lung Cancer Social Media #LCSM community and related chats)," the investigators wrote.

The National Science Foundation supported parts of this research.

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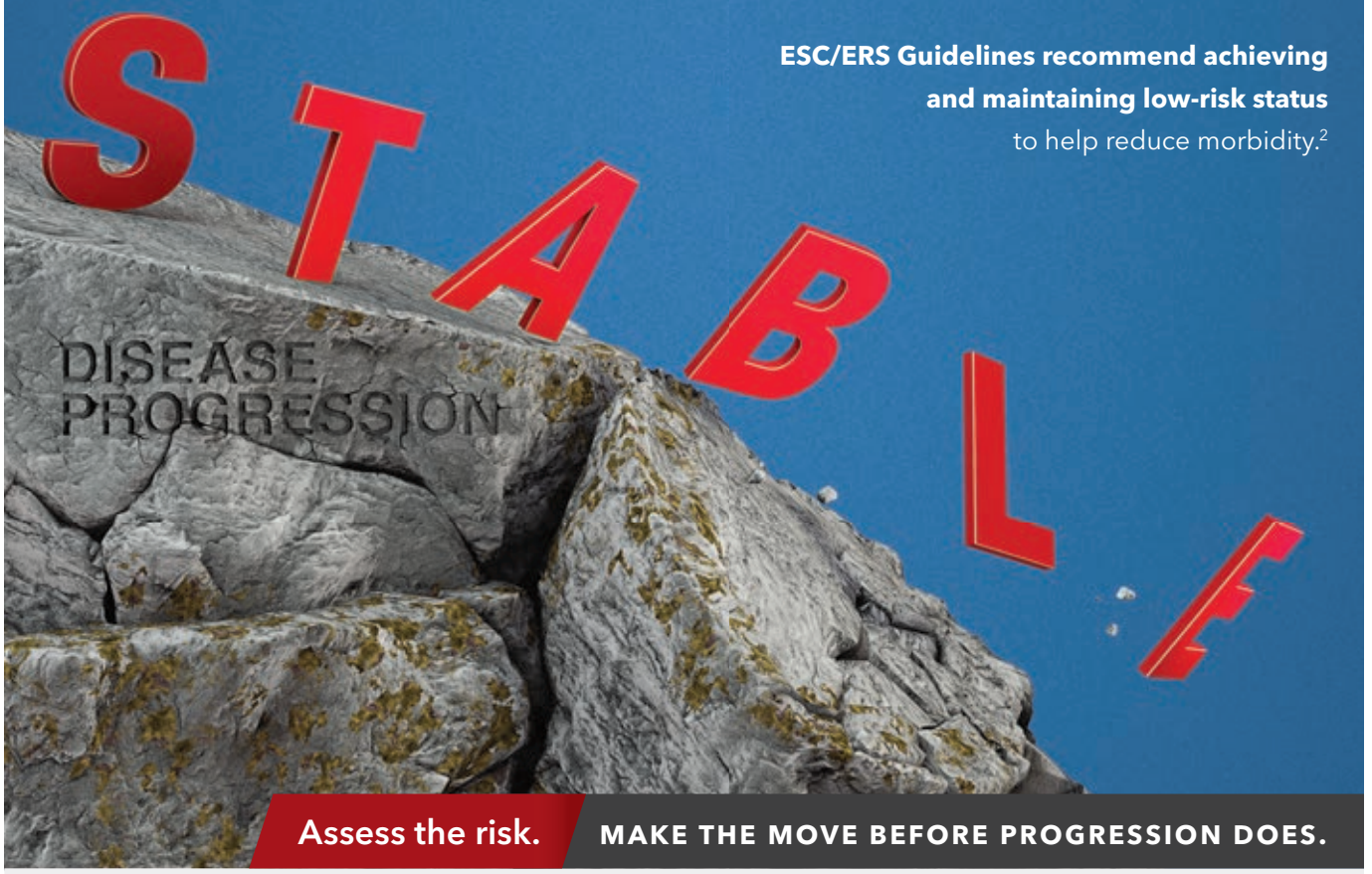
SOURCE: Sutton J et al. J Am Coll Radiol. 2018 Jan. doi: 10.1016/j.jacr.2017.09.043.

IN PULMONARY ARTERIAL HYPERTENSION (PAH)

HOW STABLE IS STABLE?

43% of FC II patients (401/925) clinically worsened* in the first year of follow-up
after enrollment in the REVEAL Registry, compared with 45% of FC III patients (625/1399).[1]

ESC/ERS Guidelines recommend achieving and maintaining low-risk status
to help reduce morbidity.[2]



Assess the risk. MAKE THE MOVE BEFORE PROGRESSION DOES.

*Clinical worsening was defined as worsening New York Heart Association FC, a ≥15% reduction in 6-minute walk distance, all-cause hospitalization, or the introduction of a parenteral prostacyclin analog for any reason. Excludes patients who died or had a major event without a worsening event.[1]

REVEAL (Registry to EValuate Early And Long-term PAH Disease Management) was a US-based, observational registry involving 55 academic and community-based treatment centers. 3515 patients enrolled between March 2006 and December 2009. Analysis included overall 2-year survival and survival free from major events. Population for this analysis was 3001 patients.[1,3] REVEAL was funded and sponsored by Actelion Pharmaceuticals US, Inc.

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ERS=European Respiratory Society; ESC=European Society of Cardiology; FC=functional class.

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Follow-up CTs nonsuperior to x-rays in NSCLC

BY NEIL OSTERWEIL
Frontline Medical News

MADRID – Computed tomography scans do not appear to be superior to plain old chest x-rays for follow-up of patients with completely resected non–small cell lung cancer (NSCLC), results of a randomized clinical trial suggest.

Among 1,775 patients followed out to 10 years with either a "minimal" protocol – consisting of history, physical exam, and periodic chest x-rays – or a "maximal" protocol – including CT scans of the thorax and upper abdomen, as well as bronchoscopy for squamous-cell carcinomas – there were no significant differences in overall survival at either 3, 5, or 8 years of follow-up, reported Virginie Westeel, MD, from the Centre Hospitalier Régional Universitaire of the Hôpital Jean Minjoz in Besançon, France.

"Most clinical practice guidelines recommend follow-up after resection for non–small cell lung cancer, including clinic visits with history and physical examination with chest x-rays every 6 to 12 months for 2 years and then yearly. This recommendation relies on expert opinion and small prospective series, but there [were] until now no randomized controlled trials to answer this question," she said at a briefing at the European Society of Medical Oncology Congress.

In hopes of finding that answer, Dr. Westeel and colleagues in the French Cooperative Thoracic Oncology Group conducted a clinical trial comparing the standard follow-up approach recommended in most clinical guidelines, as described by Dr. Westeel, with an experimental protocol consisting of history and exam plus chest x-ray, CT scans, and fiber-optic bronchoscopy (mandatory for squamous- and large-cell carcinomas, optional for adenocarcinomas).

Patients with completely resected stage I, II, and IIIA tumors, and T4 tumors with pulmonary nodules in the same lobe, were randomly assigned to follow-up with one of the two protocols.

In each trial arm, the assigned procedures were repeated every 6 months after randomization for the first 2 years, then yearly until 5 years.

After a median follow-up of 8.7 years, there was no significant difference in the primary endpoint of overall survival. Median OS was 123.6 months in the maximal protocol group, compared with 99.7 months in the minimal protocol group ($P = .037$)

The 3-, 5-, and 8-year survival rates for the maximal and minimal protocols, respectively, were 76.1% vs. 77.3%, 65.8% vs. 66.7%, and 54.6% vs. 51.7%.

Because there appeared to be a separation of the survival curve beginning around 8 years, the investigators performed an exploratory 2-year landmark analysis.

They found that, among patients who had a recurrence within 24 months of randomization, there was no difference in OS between each follow-up protocol. However, among those patients with no recurrence within 24 months of resection, the median OS was not reached among patients assigned to the maximal protocol versus 129.3 months for those assigned to the minimal protocol ($P = .04$).

Patients without early recurrence had higher rates of secondary primary cancers, and for these patients, early detection with CT-based surveillance could explain the differences in overall survival, Dr. Westeel said.

"Our suggestion for practice is that, because there is no survival difference, both follow-up protocols are acceptable. However, a CT scan every 6 months is probably of no value in the first 2 years," but yearly chest CTs to detect second primary cancers early may be of interest, she said.

Enriqueta Felip, MD, from Vall D'Hebron Institute of Oncology in Barcelona, who was not involved in the trial, commented that, while the study needed to be conducted, it was unlikely to change her clinical practice because of potential differences among patients with varying stages of NSCLC at the time of resection.

"I think it's an important trial, [but] tomorrow I will follow my patients with a CT scan," she said.

FRONTLINE MEDICAL NEWS

"Most clinical practice guidelines recommend follow-up after resection for non–small cell lung cancer," said Dr. Virginie Westeel.

Dr. Felip was an invited expert at the briefing.

The study was supported by the French Ministry of Health, Fondation de France, and Laboratoire Lilly. Dr. Westeel and Dr. Felip reported no conflicts of interest relevant to the study.

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States show large disparities in lung cancer mortality

BY RICHARD FRANKI
Frontline Medical News

Mortality from lung cancer is expected to be close to 50 per a population of 100,000 in 2018, with the highest rate in West Virginia and the lowest in Utah.

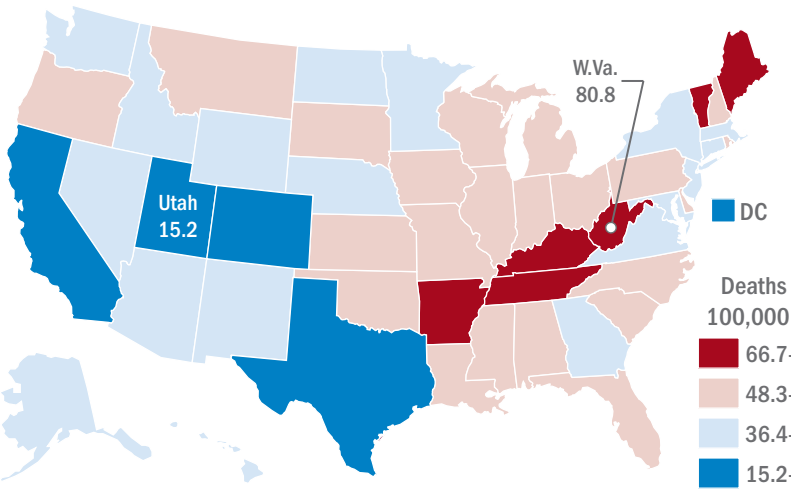
Approximately 154,050 deaths from lung cancer – three times as many as any other cancer – are predicted for the year in the United States by the American Cancer Society in its Cancer Facts & Figures 2018, based on analysis of 2001-2015 data from the National Center for Health Statistics. That figure is down from the 155,870 predicted for 2017, as the most recent trend (2011-2015) in the death rate has been a decline of about 2.3% per year for women and 3.8% per year for men, the ACS noted.

The expected number of deaths for 2018, coupled with a current population estimate of nearly 326 million, works out to an expected death rate of 47.3 per a population of 100,000. The Census Bureau estimates for the state populations and the deaths projected by the ACS produce expected death rates of 80.8 per 100,000 for West Virginia and 15.2 for Utah. Kentucky's rate of 79.3 is just behind West Virginia, but Colorado, the next-lowest state after Utah, has an estimated rate that's almost twice as high at 28.5.

Nationally, death rates for lung cancer were 53.8 per 100,000 for males and 35.4 for females for 2011-2015, and incidence rates were 73 per 100,000 for males and 52.8 for females for 2010-2014, the ACS reported.

Among racial and ethnic groups, in men, the mortality was highest for those who were both non-Hispanic and black (66.9 per 100,00) during 2011-2015. Of the racial and ethnic groups of women for the same period, white women had the highest death rate (39). Hispanic/Latino men (26.4) and Hispanic/Latino women (13.3) had the lowest deaths rates, according to the report.

Estimated lung cancer death rates for 2018



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Note: Based on 2001-2015 mortality data from the National Center for Health Statistics.
Source: American Cancer Society

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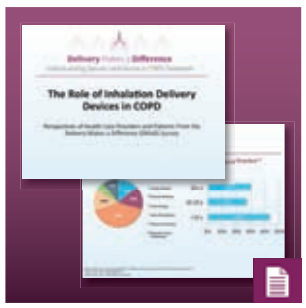

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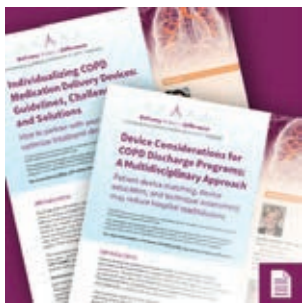

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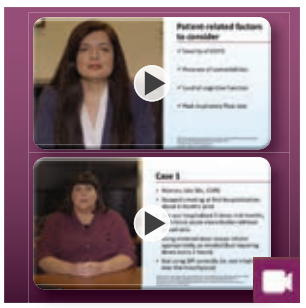

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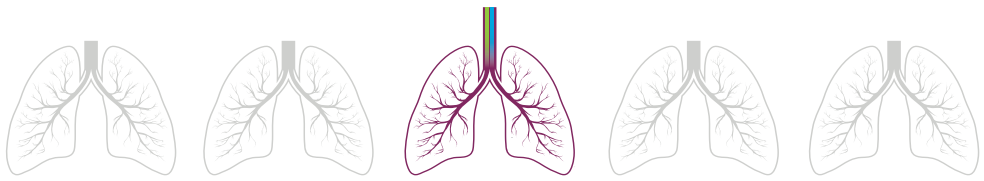

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Reference: 1. Hanania NA, Braman S, Adams SG, et al. The role of inhalation delivery devices in COPD: perspectives of patients and health care providers. Submitted manuscript.

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New multi-analyte blood test shows promise in screening for several common solid tumors

BY SHANNON AYMES
Frontline Medical News

Imagine a single blood test that would cost less than $500 and could screen for at least eight cancer types.

It's early days for the technology, called CancerSEEK, but the test had a sensitivity of 69%-98%, depending on the cancer type, and a specificity of 99% in a cohort of 1,005 patients with stage I-III cancers and 850 healthy controls, wrote Joshua D. Cohen of the Ludwig Center for Cancer Genetics and Therapeutics at Johns Hopkins University, Baltimore, and his colleagues. The report was published in Science.

CancerSEEK tests for mutations in 2,001 genomic positions and eight proteins. The researchers examined a 61-amplicon panel with each amplicon analyzing an average of 33 base pairs within a gene. They theorized the test could detect between 41% and 95% of the cancers in the Catalog of Somatic Mutations in Cancer dataset. They next used multiplex-PCR techniques to minimize errors associated with large sequencing and identified protein biomarkers for early stage cancers that may not release detectable ctDNA.

The researchers used the technology to examine blood samples from 1,005 patients with stage I (20%), stage II (49%), or stage III (31%) cancers of the ovary, liver, stomach, pancreas, esophagus, colorectum, lung, or breast prior to undergoing neoadjuvant chemotherapy. Participants had a median age of 64 years (range of 22-93 years). The healthy controls did not have a history of cancer, chronic kidney disease, autoimmune disease, or high-grade dysplasia.

The sensitivity of the test ranged from 98% in ovarian cancer to 33% in breast cancer, but the specificity was greater than 99% with only 7 of 812 control participants having a positive result. "We could not be certain that the few 'false positive' individuals identified among the healthy cohort did not actually have an as-yet undetected cancer, but classifying them as false positives provided the most conservative approach to classification and interpretation of the data," the authors wrote.

When tumor tissue samples from 153 patients with statistically significant ctDNA levels were analyzed, identical mutations were found in the plasma and tumor in 90% (138) of all cases.

Based on cancer stage, sensitivity for stage I cancers was 43%, for stage II 73%, and for stage III 78%. Again, sensitivity varied depending on cancer type, with 100% sensitivity for stage I liver cancer and 20% sensitivity for stage I esophageal cancer.

When tumor tissue samples from 153 patients with statistically significant ctDNA levels were analyzed, identical mutations were found in the plasma and tumor in 90% (138) of all cases.

The protein markers in the CancerSEEK test might also be able to anatomically locate malignancies. Using machine learning to analyze patients testing positive with CancerSEEK, the results narrowed the source of the cancer to two possible anatomical sites in approximately 83% of patients and to one anatomical site in approximately 63% of patients. Accuracy was highest for colorectal cancer and lowest for lung cancer.

"We could not be certain that the few 'false positive' individuals identified among the healthy cohort did not actually have an as-yet undetected cancer, but classifying them as false positives" was most conservative.

As the study included otherwise healthy patients with known malignancies, the results need to be confirmed with prospective studies of incidence cancer types in a large population. Patients in the screening setting may have less advanced disease and other comorbidities that could impact the sensitivity and specificity of the CancerSEEK test, the researchers wrote.

The study was funded by multiple sources including grants from the National Institutes of Health. The authors reported various disclosures involving diagnostics and pharmaceutical companies.

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SOURCE: Cohen JD et al., Science. 2018 Jan 18. doi: 10.1126/science.aar3247.

What are the clinically relevant questions answered by this test?

Molecular panels are here to stay – and the GI community will in some shape or form be impacted, be it in performing diagnostic procedures on test-positive patients, or risk-stratifying patients prior to testing.

The conceptual challenge is that it is not about what any given test measures – various panels use separate combination of markers from epigenetics to DNA mutations as well as whole or truncated proteins – but how well a specific test with its somewhat arbitrarily chosen components and cutoffs performs. And, more importantly, what the clinical implications of positive or negative test results are. And no one knows that. At least for now.

A recent report in Science from a group from the Ludwig Center for Cancer Genetics at Johns Hopkins proposes a new cancer blood test based on a very systematic and thoughtful approach to include select mutations in cell-free DNA and circulating proteins associated with various solid organ tumors. For validation, they used healthy and advanced but nonmetastatic cancer cohorts. Through stringent controls and a series of validations, the authors present a range of sensitivities for the various cancer types with an impressive specificity. This is a technically very strong approach with many nifty and thoughtful additions to give this test a very promising first foray – did anybody watch CNN?

DR. JUNG

While not ready for prime time, which is a tall order for a first report, the authors dutifully point out the need for a prospective real life cohort validation. In the meantime, regardless of the outcome of this particular test, it is a repeated reminder that we need to stay abreast of the advances and the details of each molecular test, especially with a likely very diverse and distinct group of tests to choose from.

Many of us will be part of interpreting results and determining further management. Just as with hereditary cancer genetic panel testing, our technical ability may have stretched beyond our ability to fully understand the implications. Many questions will arise: What about true false positives? False negatives? Intervals? Can such tests replace other screening? How to choose any given test over the other? Should tests be combined or alternated? The tests will be technically refined and are here to stay – we need to get to work on finding answers to the clinically relevant questions.

Barbara Jung, MD, is the Thomas J. Layden Endowed Professor and chief of the division of gastroenterology and hepatology, University of Chicago.

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Elderly at highest CV risk get short-statined

BY BRUCE JANCIN
Frontline Medical News

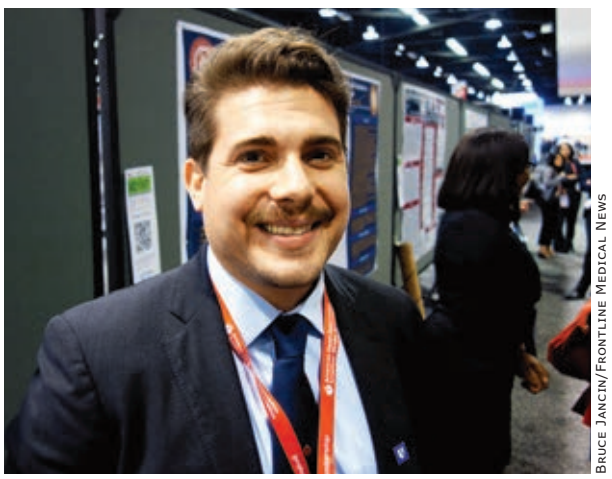
ANAHEIM, CALIF. – Adults older than age 75 years with known atherosclerotic cardiovascular disease are significantly less likely than younger patients to receive a high-intensity statin for secondary prevention, even though they actually tolerate statin therapy better, Michael G. Nanna, MD, said at the American Heart Association scientific sessions.

This was among the eye-opening findings from his analysis of data from the PALM (Patient and Provider Assessment of Lipid Management) Registry, a national registry that provides a snapshot of how cardiologists, primary care physicians, and endocrinologists in real-world community practice care for their patients with known atherosclerotic cardiovascular disease (ASCVD) or at high risk for it.

The analysis included 7,736 patients receiving care in 138 U.S. cardiology, primary care, and endocrinology practices, including 1,704 patients over age 75, 1,038 of whom had known ASCVD and thus were candidates for secondary prevention measures, explained Dr. Nanna, a second-year cardiology fellow at Duke University in Durham, N.C.

The impetus for this study was the dearth of information about what's going on in everyday clinical practice in terms of statin utilization and side effects in the elderly since release of the 2013 American College of Cardiology and American Heart Association cholesterol guidelines. Those guidelines highlighted the lack of randomized clinical trial data to support the use of statins in patients over age 75, who had typically been excluded from participation in the major studies.

The guidelines recommended moderate-intensity statin therapy for secondary prevention in the elderly, and didn't take a firm position regarding statins for primary prevention in older patients.



Bruce Jancin/Frontline Medical News

Dr. Michael G. Nanna said, "My dream is that studies like this will motivate folks to fund a randomized clinical trial looking at high-intensity statins in older adults."

What's happening in community practice

For primary prevention in the elderly, physicians appear to be extrapolating from their practice patterns in younger at-risk patients. Sixty-three percent of patients younger than age 75 at high risk for ASCVD were on a statin for primary prevention, as were an equal percentage of older patients. Moreover, 10.2% of older patients were on a high-intensity statin for primary prevention, a rate not significantly different from the 12.3% in younger at-risk patients.

Statin therapy for secondary prevention in the elderly was a different story. Older patients were significantly less likely to receive any statin for secondary prevention. And they were much less likely to get a high-intensity statin, by a margin of 23.5%-36.2%.

Indeed, in a multivariate regression analysis adjusted for patient demographics, diabetes, smoking, heart failure, body mass index, insurance type, income, and whether a patient saw a cardiologist, older patients with ASCVD were 42% less likely to receive a high-intensity statin than patients younger than age 75.

"It's interesting that older patients who have ASCVD are actually the group at highest risk of events, yet they're the least likely to receive a high-intensity statin," Dr. Nanna observed in an interview.

Of note, older patients were significantly less likely to report any side effect on a statin, by a margin of 41.3%-46.6%. They were also markedly less likely to report myalgias, by a margin of 23.3%-33.3%.

"One of the reasons why folks have shied away from treating older patients with statins, and especially with high-intensity statins, is the theoretical risk of more side effects and drug interactions. We didn't see that," Dr. Nanna said.

What's next

"My dream is that studies like this will motivate folks to fund a randomized clinical trial looking at high-intensity statins in older adults," Dr. Nanna said. "I think there are funding challenges because both rosuvastatin and atorvastatin are generic at this point. But I think it needs to be done."

Rumor has it, he added, that the first randomized trial of statin therapy in the elderly will be in the primary prevention setting. "That's an area where we're all essentially operating in an evidence-free zone," Dr. Nanna said.

Regeneron and Sanofi fund the PALM Registry. Dr. Nanna reported having no relevant financial disclosures.

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FDA approves implantable therapy for PAH

BY LORI LAUBACH
Frontline Medical News

The Food and Drug Administration announced that it has approved an implantable system for treprostinil to treat adult patients with New York Heart Association (NYHA) Class I, II, and III pulmonary arterial hypertension.

This infusion system is implanted into a patient for intravenous delivery of treprostinil (Remodulin) and is designed to help supply blood to the lungs and keep a patient's blood pressure within a healthy range. The system comprises three parts: the pump, the programmer, and the catheter.

The Medtronic 8201 Implantable 80 cm Intravascular Catheter is inserted through a vein at the superior cavoatrial junction and connects the catheter to the Medtronic SynchroMed II 8637P Programmable Pump in a pump pocket placed beneath the abdominal skin. Then, the surgeon uses the Medtronic N'Vision 8840 Clinician Programmer with 8870 Application Card to program and review the pump's settings. Once programmed, the implantable system delivers the Remodulin injection from the pump reservoir, through the pump tubing, the catheter port, and the catheter to the intravascular delivery site. Finally, the pump stays permanently implanted and the health care provider uses a needle and syringe refill kit to refill the pump with Remodulin, as needed.

Read the full approval on the FDA's website.

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Try thrombolysis for caval extension of iliofemoral DVT

BY BRUCE JANCIN
Frontline Medical News

CHICAGO – Caval extension of an acute iliofemoral deep vein thrombosis paradoxically portends better treatment outcomes than does thrombolysis of a DVT without involvement of the inferior vena cava, said Rabih A. Chaer, MD, professor of surgery at the University of Pittsburgh.

This finding from a retrospective analysis of the University of Pittsburgh experience might seem counterintuitive. After all, caval extension clearly indicates a greater clot burden. One possible explanation: Clearing a thrombus from a large vessel, such as the inferior vena cava (IVC), provides an added protective effect. Also, since the caval segments don't have valves – their flow is based upon negative pressure in the chest – they may not contribute as much to postthrombotic morbidity to the same extent as do thrombosed iliofemoral segments, Dr. Chaer speculated at a symposium on vascular surgery sponsored by Northwestern University.

In addition, patients with caval extension were treated more aggressively: 98% of them underwent pharmacomechanical thrombolysis with the Angiojet or another device as an adjunct to catheter-directed thrombolysis, compared with 82% of noncaval patients.

The impetus for Dr. Chaer and coinvestigators to review the Pittsburgh experience was a lack of clarity in the

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Continued from page 36

literature as to the effect IVC thrombosis has on thrombolysis outcomes in patients with acute iliofemoral DVT. Even though caval thrombus extension is present in up to 22% of patients with iliofemoral DVT, current guidelines issued by the American College of Chest Physicians, the American Heart Association, and the Society for Vascular Surgery don't address the distinction between iliofemoral DVT with and without IVC extension in regard to the occurrence of postthrombotic syndrome (PTS), the most common complication of DVT.

The incidence of PTS in patients whose iliofemoral DVT is treated

BRUCE JANCIN/FRONTLINE MEDICAL NEWS

Dr. Rabih A. Chaer said lack of clarity in the literature led to the review.

by anticoagulation and compression alone is up to 50%. Mounting evidence indicates that catheter-directed thrombolysis and pharmacomechanical thrombolysis aimed at achieving early thrombus removal and symptom relief help maintain valvular competence and reduce the risk of PTS, the surgeon noted.

PTS is diagnosed using the validated Villalta scale, which incorporates clinical signs including pain on calf compression, skin edema and redness, and ulcers, as well as symptoms such as leg cramping, heaviness, itching, and paresthesia.

The Pittsburgh series included 102 consecutive patients treated with various combinations of catheter-directed or pharmacomechanical thrombolysis in 127 limbs with acute iliofemoral thrombosis. In 46 patients, the thrombus extended into the IVC, all the way up to the renal veins in most cases.

The groups with and without caval extension were similar in terms of age and prevalence of malignancy, hypercoagulable state, and clot age. However, a history of previous DVT was significantly more common in the group with IVC thrombus. Also, more than 60% of patients with caval extension got an IVC filter, a rate more than 10-fold greater than that in patients without caval extension.

In this series, caval thrombosis had no effect on the technical success of thrombolysis. The technical success rate – defined as at least 50% clot lysis – was 89% in both groups. Rates of recurrent DVT within 30 days were similar in the two groups as well: 11% in the caval thrombosis group and 14% in the noncaval group. At 2 years post intervention, 77%-78% of patients in both groups remained free of DVT recurrence. The rate of PTS – defined by a Villalta score of 5 or more – at 2 years was 34% in the noncaval group, which was significantly higher than the 11% rate in patients with IVC thrombus extension.

On multivariate analysis, incomplete clot lysis was associated with nearly a 23-fold increased risk of recurrent DVT and a 5.6-fold increased risk of PTS. Caval involvement was independently associated with a 78% reduction in PTS risk.

The Society for Vascular Surgery's guidelines recommend pharmacomechanical thrombolysis over

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catheter-directed thrombolysis if the expertise is available.

"Pharmacomechanical techniques can be advantageous. They can expedite the lysis process by clearing most of the clot. In our series, 20 patients were treated with pharmacomechanical techniques in a single session," Dr. Chaer noted.

The use of IVC filters in the setting of caval extension of iliofemoral DVT is controversial: A thrombus that gets trapped in the filter is tough to remove, precluding successful recanalization.

"One-third of the patients in our series got a filter, but we've become more conservative nowadays. We don't use filters anymore. But I think those patients who might benefit from an IVC filter are those who present with a PE [pulmonary embolism], because that's telling you they might develop another PE, as well as those patients in whom pharmacomechanical thrombolysis is anticipated because we've seen that those patients are also more likely to develop a PE," he said.

The University of Pittsburgh study on the effect of IVC thrombus extension has been published (J Vasc Surg Venous Lymphat Disord. 2016 Oct;4[4]:385-91).

Dr. Chaer reported serving as a paid speaker for Boston Scientific.

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SOURCE: Chaer RA. Northwestern Vascular Symposium 2017.

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Benefit of dabigatran over warfarin persists

BY M. ALEXANDER OTTO
Frontline Medical News

ANAHEIM, CALIF. – The benefit of dabigatran dual therapy versus warfarin triple therapy after percutaneous coronary intervention in patients with atrial fibrillation was consistent whether patients had drug-eluting or bare-metal stents, concomitant treatment with ticagrelor or clopidogrel, or acute coronary syndrome or stable disease as the indication for PCI, according to a subgroup analysis of the RE-DUAL PCI trial.

The trial, presented at the American Heart Association scientific sessions, randomized 2,725 patients to triple therapy with warfarin plus a P2Y12 inhibitor (clopidogrel or ticagrelor) and aspirin – the triple-therapy group – or dabigatran 110 mg or 150 mg twice daily plus clopido-

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The incidence of the composite efficacy endpoint was 13.7% in the two dual-therapy groups, compared with 13.4% in the group that received triple therapy.

DR. OLDGREN

grel or ticagrelor – the dual-therapy groups (N Engl J Med. 2017 Oct 19;377[16]:1513-24).

After a mean follow-up 14 months, the incidence of the major or clinically relevant nonmajor bleeding was 15.4% in the 110-mg dual-therapy group (hazard ratio, 0.52; 95% confidence interval, 0.42-0.63; *P* less than .001) and 20.2% in the 150-mg dual-therapy group (HR, 0.72; 95% CI, 0.58-0.88; *P* less than .001), versus about 26% with triple therapy.

The incidence of the composite efficacy endpoint – death, unplanned revascularization, myocardial infarction, stroke, or systemic embolism – was 13.7% in the two dual-therapy groups versus 13.4% with triple therapy (HR, 1.04; 95% CI, 0.84-1.29; *P* = .005).

The investigators found consistent results when they analyzed their prespecified subgroups.

Acute coronary syndrome (ACS) was the indication for PCI in about half the patients; the rest had stable coronary artery disease. The two groups were well balanced except ACS patients were more likely to be new to oral anticoagulation. Results were consistent with the main trial in terms of bleeding. There was a trend for more embolic events in ACS patients on dabigatran 110 mg, but it was not significant, said investigator Jonas Oldgren, MD, of Uppsala (Sweden) University.

Drug-eluting stents were placed in 83% of patients; the rest had bare metal stents (BMS). The groups were well-balanced, except BMS patients were again more likely to be new to oral anticoagulation. Bleeding, thromboembolic events, and mortality were consistent with the main results regardless of the stent type, Most of the subjects were on clopidogrel, with just 12% on ticagrelor in both the dabigatran and warfarin groups. Ticagrelor patients were more likely to have ACS as their PCI indication and be new to oral anticoagulation. Ticagrelor patients were also more clinically complex, with a higher bleeding risk. Even so, they had relative bleeding risk reduction and efficacy results with dabigatran that were consistent with the overall finding, Dr. Oldgren said.

Patients were eligible for RE-DU-AL PCI (Evaluation of Dual Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients with AF That Undergo a PCI With Stenting) if they had nonvalvular atrial fibrillation and a successful PCI within 120 hours. Those with bioprosthetic or mechanical heart valves, severe renal insufficiency, or other major comorbidities were excluded.

The trial was funded by Boehringer Ingelheim, the maker of dabigatran.

Several investigators were employees. Dr. Oldgren is an adviser to Boehringer Ingelheim. Other authors reported financial ties to the company as well.

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Guidelines call for drugs for diabetes with CVD

BY MICHELE G. SULLIVAN
Frontline Medical News

Recent studies that confirm the cardiovascular benefit of some anti-hyperglycemic agents are shaping the newest therapeutic recommendations for patients with type 2 diabetes and comorbid atherosclerotic cardiovascular disease (ASCVD).

Treatment for these patients – as all with diabetes – should start with lifestyle modifications and metformin. But in its new position statement, the American Diabetes Association now recommends that clinicians consider adding agents proved to reduce major cardiovascular events and cardiovascular death – such as the sodium glucose cotransporter-2 (SGLT2) inhibitor empagliflozin or the glucagon-like peptide 1 (GLP-1) agonist liraglutide – to the regimens of patients with diabetes and ASCVD (Diabetes Care. 2018;41[Suppl. 1]:S86-104. doi: 10.2337/dc18-S009).

Clinicians may also consider adding these agents for cardiovascular benefit alone.

DR. KALYANI

The medications are indicated if, after being treated with lifestyle and metformin therapy, the patient isn't meeting hemoglobin A1c goals, said Rita R. Kalyani, MD, who led the ADA's 12-member writing committee. But clinicians may also consider adding these agents for cardiovascular benefit alone, even when glucose control is adequate on a regimen of lifestyle modification and metformin, with dose adjustments as appropriate, she said in an interview.

"A1c remains the main target of sequencing antihyperglycemic therapies, if it's not reached after 3 months," said Dr. Kalyani of Johns Hopkins University, Baltimore. "But, it could also be that the provider, after consulting with the patient, feels it's appropriate to add one of these agents solely for cardioprotective benefit in patients with ASCVD."

The recommendation to incorporate agents with cardiovascular benefit is related directly to data from two trials, LEADER and EMPA-REG, which support this recommendation. All of these cardiovascular outcome trials included a majority of patients who were already on metformin. "We developed these evidence-based recommendations based on these trials and to appropriately reflect the populations studied," said Dr. Kalyani.

The ADA's "Standards of Medical Care in Diabetes 2018" is the first position statement from any professional society to provide specific recommendations for the incorporation of these newer antihyperglycemic agents for their cardioprotective benefit in the treatment algorithm for type 2 diabetes. But the document provides much more than an algorithm for treating patients with concomitant ASCVD, Dr. Kalyani said. It is a comprehensive clinical guide covering recommendations for diagnosis, medical evaluation, comorbidities, lifestyle change, cardiovascular risk management, and treating diabetes in children and teens, pregnant women, and patients with hypertension.

"This is a nice enhancement of previously published guidelines for diabetes therapy."

DR. JELLINGER

The 2018 update contains a number of new recommendations; more will be added as new data emerge, since the ADA intends it to be a continuously refreshed "living document." This makes it especially clinically useful, Paul S. Jellinger, MD, said in an interview. A member of the writing committee of the American Association of Clinical Endocrinologists' diabetes management guidelines, Dr. Jellinger feels ADA's previous versions have not been as targeted as this new one and, he hopes, its subsequent iterations.

"This is a nice enhancement of previously published guidelines for diabetes therapy," said Dr. Jellinger, professor of clinical medicine at the University of Miami. "For the first time, ADA is providing some guidance in terms of which agents to use. It's definitely more prescriptive than it was in the past, when, unlike the AACE Diabetes Guidelines, it was a palette of choice for clinicians, but with very little guidance about which agent to pick. The guidance for patients with cardiovascular disease in particular is big news because these antihyperglycemic agents showed such a significant cardiovascular benefit in the trials."

While the document gives a detailed algorithm of advancing therapy in patients with ASCVD, it doesn't specify a preference for a specific drug class after metformin therapy in patients without ASCVD. Instead, it provides a detailed table listing the drug-specific effects and patient factors to consider when selecting from different classes of antihyperglycemic agents (SGLT2 inhibitors, GLP-1 agonists, DPP-4 inhibitors, thiazolidinones, sulfonylureas, and insulins). The table notes the drugs' general efficacy in diabetes, and their impact on hypoglycemia, weight gain, and cardiovascular and renal health. The table also includes the Food and Drug Administration black box warnings that are on some of these medications.

"[Providers] have a responsibility to ask if a patient is not taking certain medications because of the cost."

DR. HELLMAN

Another helpful feature is a cost comparison of antidiabetic agents, Dr. Kalyani noted. "Last year we added comprehensive cost tables for all the different insulins and noninsulins, and this year we added a second data set of cost information, to assist the provider when prescribing these agents."

The pricing information is a very important addition to this guideline, and one that clinicians will appreciate, said Richard Hellman, MD, clinical professor of medicine at the University of Missouri–Kansas City.

"In this document, ADA is urging providers of care to ask about whether the cost of their diabetes care is more than they can deal with. They present tables which compare the costs of the current blood glucose lowering agents used in the U.S., and it is plain to see that many patients, without insurance coverage, will find some of the medications unaffordable," said Dr. Hellman, a past president of AACE. "They also provide data that show half of all patients with diabetes have financial problems," and he suspects that medication costs are an important component of their financial insecurity.

The document also notes data from the 2017 National Health and Nutrition Examination Survey, which found that 10% of people with diabetes have severe food insecurity and 20% have mild food insecurity (Diabetes Educ. 2017;43:260-71. doi: 10.1177/0145721717699890).

"Another thing the document points out is that two-thirds of the patients who don't take all their medications due to cost don't tell their doctor," Dr. Hellman said. "The ADA is making the point that providers have a responsibility to ask if a patient is not taking certain medications because of the cost. We have so many better tools to manage this disease, but so many of these tools are unaffordable."

While the treatment algorithm for patients with ASCVD will likely be embraced, another new recommendation may stir the pot a bit, Dr. Hellman noted. The section on cardiovascular disease and risk management sticks to a definition of hypertension as 140/90 mm Hg or higher – a striking diversion from the new 130/80 mm Hg limit set this fall by both the American Heart Association and the American College of Cardiology.

"This difference in recommendations is very important and will be controversial," Dr. Hellman said, adding that he agrees with this clinical point.

Again, this recommendation is grounded in clinical trials, which suggest that people with diabetes don't benefit from overly strict blood pressure control. The new AHA/ACC recommendations largely drew on data from SPRINT, which was conducted in an entirely nondiabetic population. "These gave a clear signal that a lower BP target is beneficial to that group," Dr. Hellman said.

But large well-designed randomized controlled trials of intensive blood pressure lowering in people with diabetes, such as ACCORD-BP, did not demonstrate that intensive blood pressure lowering targeting a systolic less than120 mm Hg had a significant benefit on the composite primary cardiovascular endpoint.

Dr. Kalyani and Dr. Hellman had no financial disclosures. Dr. Jellinger has been a speaker for several pharmaceutical companies.

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SOURCE: Kalyani R et al. Diabetes Care. 2018;41(Suppl. 1):S86-104. doi: 10.2337/dc18-S009.

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MedPAC: Medicare hospital readmissions program is working

BY GREGORY TWACHTMAN
Frontline Medical News

WASHINGTON – The Medicare Hospital Readmissions Reduction Program is working, according to an original analysis of Medicare claims data presented at a meeting of the Medicare Payment Advisory Commission.

"First, readmissions declined," MedPAC staff member Jeff Stensland, PhD, said during a congressionally mandated staff report to the commissioners. "Second, while observation stays increased, they did not fully offset the decrease in readmissions. Third, while [emergency department] visits also increased, those increases appear to largely be due to factors other than the readmission program. And fourth, in addition, all the evidence we examined suggests that the readmissions program did not result in increased mortality."

While the program is "not perfect, it has appeared to generate some benefits for patients and taxpayers," including a reduction in readmissions and patients spending less time in the hospital with "at least equal outcomes," Dr. Stensland said at the meeting.

Taxpayers benefited from a $2 billion reduction in spending on readmissions, which will "help extend the viability of the Medicare Trust Fund." He noted that improvements to the program will be discussed at future MedPAC meetings.

Not all MedPAC commissioners agreed with the staff analysis.

"It just leaves me with a slightly different conclusion, though,

"There were good things that happened with the readmission penalty [but] clearly there were other things going on."

DR. REDBERG

because I think it's really hard to know what's going on here," said Rita Redberg, MD, of the University of California, San Francisco. "It's all observational data. There are questions about temporal trends, other programs going on. I mean, clearly there were good things that happened with the readmission penalty. Hospitals started outpatient programs, pharmacists, nurse to call the patient, but then clearly there were other things going on. And some things are just not preventable, and it may have created perverse incentives not to readmit patients. We don't know."

David Nerenz, PhD, of the Henry Ford Health System, Detroit, also was not convinced the program was having an impact, noting that hospital readmissions began to decline even before the program started.

In looking at a graph presented that showed this trend, "I was impressed by the fact that the trend line started coming down all the way to the left side of the graph, and what my eye was impressed with was more just the continuation rather than a change, so I guess I feel cautious saying the program had certain effects because they certainly don't jump off the graph visually," Dr. Nerenz said. "I'm not disputing the numbers, but to say just as a clear unqualified conclusion the program reduced readmissions, I'm not so sure."

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VIEW ON THE NEWS

Michael E. Nelson, MD, FCCP, comments: It is likely premature to make any firm conclusions about how effectively this program decreases unnecessary utilization of hospitals. However, it is heartening to know that it did not increase mortality. The one variable that would best control readmissions is patient education. What constitutes an emergency requiring hospital evaluation and potential admission is often not explained to the patient by you and me.

Health care gets little attention in State of the Union

BY GREGORY TWACHTMAN
Frontline Medical News

President Trump reaffirmed his campaign promise to lower prescription drug prices during his first State of the Union address – but gave no details on how he plans to do so.

"One of my greatest priorities is to reduce the price of prescription drugs," President Trump said in his Jan. 30 address to a joint session of Congress. "In many other countries, these drugs cost far less than what we pay in the United States, and it is very, very unfair. That is why I have directed my administration to make fixing the injustice of high drug prices one of my top priorities for the year."

He then emphatically stated: "Prices will come down substantially. Watch."

His words followed the confirmation of Alex Azar as Health & Human Services secretary. Mr. Azar's nomination was criticized by some who questioned whether the former president of Eli Lilly's U.S. operations could be effective at tackling the surging prices of pharmaceuticals.

President Trump also expressed his support for allowing terminally ill patients to access experimental drugs prior to Food and Drug Administration approval, the so-called right to try.

"We also believe that patients with terminal conditions, terminal illness, should have access to experimental treatment immediately that could potentially save their lives," he said. "People who are terminally ill should not have to go from country to country to seek a cure. I want to give them a chance right here at home. It's time for the Congress to give these wonderful incredible Americans the right to try."

The Senate passed a right to try bill (S. 204) in 2017 by unanimous consent, but the House has yet to act upon it.

President Trump reaffirmed his commitment to fighting the opioid epidemic and made a loose connection between it and his overall platform for immigration reform, saying that "these reforms will also support our response to the terrible crisis of opioid and drug addiction."

As far as addressing the epidemic itself, Mr. Trump said that his administration "is committed to fighting the drug epidemic and helping get treatment for those in need, for those who have been so terribly hurt. The struggle will be long and it will be difficult, but, as Americans always do, in the end we will succeed. We will prevail."

The president also commended Congress for effectively eliminating the Affordable Care Act's individual mandate that required people to have health insurance or suffer a financial penalty.

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President Donald J. Trump

VIEW ON THE NEWS

Michael E. Nelson, MD, FCCP, comments: As Congress nickles and dimes its way to more appropriate and affordable health care, the Presidential promises and platitudes ring somewhat hollow. There is an inherent problem with a system that spends an average of more than $10,000 per person for health care (the most for any country) but only made it to 37th place in the latest WHO Healthcare System rankings. One would think our elected officials should be able to improve on that, and yet I'm reminded of the words of George Will: "Politicians fascinate because they are such a paradox; they are an elite that accomplishes mediocrity for the public good."

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Curbs on short-term health plans could be relaxed

BY JULIE APPLEBY
Kaiser Health News

Insurers will again be able to sell short-term health insurance good for up to 12 months under a proposed rule released Feb. 20 by the Trump administration that could further roil the marketplace.

"We want to open up affordable alternatives to unaffordable Affordable Care Act policies," said Health & Human Services Secretary Alex Azar. "This is one step in the direction of providing Americans health insurance options that are more affordable and more suitable to individual and family circumstances."

The proposed rule said short-term plans could add more choices to the market at lower cost and may offer broader provider networks than Affordable Care Act plans in rural areas.

But most short-term coverage requires answering a string of medical questions, and insurers can reject applicants with preexisting medical problems, which ACA plans cannot do. As a result, the proposed rule also noted that some people who switch to them from ACA coverage may see "reduced access to some services," and "increased out of pocket costs, possibly leading to financial hardship."

The directive follows an executive order issued in October to roll back restrictions put in place during the Obama administration that limited these plans to 3 months. The rule comes on the heels of Congress' approval of tax legislation that in 2019 will end the penalty for people who opt not to carry insurance coverage.

The administration also issued separate regulations Jan. 4 that would make it easier to form "association health plans," which are offered to small businesses through membership organizations.

Together, the proposed regulations and the elimination of the so-called individual mandate by Congress could further undermine the Affordable Care Act marketplace, critics say.

Seema Verma, who now heads the Centers for Medicare & Medicaid Services, which oversees the marketplaces, told reporters Feb. 20 that federal officials believe that between 100,000 and 200,000 "healthy people" now buying insurance through those federal exchanges would switch to the short-term plans, as well as others who are now uninsured.

The new rule is expected to entice younger and healthier people from the general insurance pool by allowing a range of lower-cost options that don't include all the

MS. VERMA

benefits required by the federal law – including plans that can reject people with preexisting medical conditions. Most short-term coverage excludes benefits for maternity care, preventive care, mental health services, or substance abuse treatment.

"It's deeply concerning to me, considering the tragedy in Florida and national opioid crisis, that the administration would be encouraging the sale of policies that don't have to cover mental health and substance abuse," said Kevin Lucia, a research professor and project director at Georgetown University's Health Policy Institute.

Over time, those remaining in ACA plans will increasingly be those who qualify for premium tax credit subsidies and the sick, who can't get an alternative like a short-term plan, predict Mr. Lucia and other experts. That, in turn, would drive up ACA premiums further.

"If consumers think Obamacare premiums are high today, wait until people flood into these short-term and association health plans," said industry consultant Robert Laszewski. "The Trump administration will bring rates down substantially for healthy people, but woe unto those who get a condition and have to go back into Obamacare."

If 100,000-200,000 people shift from ACA-compliant plans in 2019, this would cause "average monthly individual market premiums … to increase," the proposed rule states. That, in turn, would cause subsidies for eligible policyholders in the ACA market to rise, costing the government $96 million–$168 million.

Supporters said the rules are needed because the ACA plans have already become too costly for people who don't receive a government subsidy to help them purchase the coverage. "The current system is failing too many," said Ms. Verma.

And, many supporters don't think the change is as significant as skeptics fear.

"It simply reverts back to where the short-term plan rules were prior to Obama limiting those plans," said Christopher Condeluci, a benefits attorney who also served as tax counsel to the U.S. Senate Finance Committee. "While these plans might not be the best answer, people do need a choice, and this new proposal provides needed choice to a certain subsection of the population."

But, in their call with reporters, CMS officials said the proposed rule seeks comment on whether there are ways to guarantee renewability of the plans, which currently cannot be renewed. Instead, policyholders must reapply and answer medical questions again. The proposal also seeks comments on whether the plans should be allowed for longer than 12-month periods.

The comment period for the proposed rule runs for 60 days. Ms. Verma said CMS hopes to get final rules out "as quickly as possible," so insurers could start offering the longer duration plans.

Short-term plans had been designed as temporary coverage, lasting for a few months while, for instance, a worker is between jobs and employer-sponsored insurances. They provide some protection to those who enroll, generally paying a percentage of hospital and doctor bills after the policyholder meets a deductible.

They are generally less expensive than ACA plans, because they cover less. For example, they set annual and lifetime caps on benefits, and few cover prescription drugs.

Most require applicants to pass a medical questionnaire – and they can also exclude coverage for preexisting medical conditions.

The plans are appealing to con-

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Congress extends CHIP, funds opioid crisis response

BY GREGORY TWACHTMAN
Frontline Medical News

Congress, despite a second shutdown in less than a month, was able to pass a number of financial extenders to fund key health care programs.

The bipartisan spending bill (H.R. 1892), passed in the early morning hours on Feb. 9 by a 71-28 vote in the Senate (16 Republicans and 12 Democrats voted against it, and Sen. John McCain [R-Ariz.] was not present) and a 240-186 vote in the House (67 Republicans and 119 Democrats voted against and 5 representatives did not vote). President Trump signed the later that morning.

The spending bill and continuing resolution to fund the government through March 23 includes $6 billion to fund treatment for opioid addiction and other mental health issues, $2 billion in additional funding for the National Institutes of Health, and 4 additional years of funding for the Children's Health Insurance Program. The additional CHIP funding extends the program for a total of 10 years.

The funding bill also made a technical correction to the Merit-Based Incentive Payment System (MIPS) track of the Medicare Quality Payment Program. It removes Part B drug reimbursement from the MIPS payment adjustment, so any positive or negative change to physician payments based on the MIPS score will be applied only to

Continued from previous page

sumers because they are cheaper than Obamacare plans. They are also attractive to brokers, because they often pay higher commissions than ACA plans. Insurers like them because their profit margins are relatively high – and are not held to the ACA requirement that they spend at least 80 percent of premium revenue on plan members' medical care.

Extending short-term plans to a full year could be a benefit to consumers because they must pass the health questionnaire only once. Still, if a consumer develops a health condition during the contract's term, that person would likely be rejected if he or she tried to renew.

Both supporters and critics of short-term plans say consumers who do develop health problems could then sign up for an ACA plan during the next open enrollment because the ACA bars insurers from rejecting people with preexisting conditions.

"We're going to have two different markets, a Wild West frontier called short-term medical … and a high-risk pool called Obamacare," said Mr. Laszewski.

KHN senior correspondent Phil Galewitz contributed to this article. Kaiser Health News is a nonprofit news service covering health issues. It is an editorially independent program of the Kaiser Family Foundation that is not affiliated with Kaiser Permanente.

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physician fee schedule payments.

The bill also repeals the Independent Payment Advisory Board, a panel created by the Affordable Care Act that would have the power to slash Medicare spending under certain budget circumstances. That board was never convened.

The funding legislation also accelerates closure of the Medicare Part D "donut hole," the coverage gap in which beneficiaries must pay 100% of medication costs prior to entering catastrophic coverage.

Just over $7 billion was provided for community health centers and Medicare's therapy caps were repealed.

While the funding bill was written in the Senate with bipartisan input and received bipartisan support, Sen. Rand Paul (R-Ky.) held up votes over objections to the more than $1 trillion it will add to the nation's debt, as well as for the fact that there was no opportunity to introduce and vote on amendments, leading to an hours-long government shutdown.

There also were concerns about two issues that could have derailed the vote in the House. Democrats wanted to add language to address immigrants brought to this nation illegally as children, while some Republicans did not want to increase the federal debt.

However, there were enough votes to pass the funding legislation.

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Lung scan often not requested for new SSc patients

BY HEIDI SPLETE
Frontline Medical News

Only half of American general rheumatologists and two-thirds of global systemic sclerosis experts routinely request high-resolution CT chest scans for all their newly diagnosed systemic sclerosis (SSc) patients despite their increased risk of interstitial lung disease, according to survey data from approximately 200 clinicians.

The researchers, led by Elana J. Bernstein, MD, of Columbia University, New York, conducted the survey because of a lack of data on how often rheumatologists order high-resolution CT for their newly diagnosed patients and the absence of clinical practice guidelines that recommend screening for interstitial lung disease (ILD) in SSc.

In a study published in Arthritis & Rheumatology, the researchers surveyed 676 American College of Rheumatology members and 356 global experts on systemic sclerosis; of these, 76 ACR general rheumatologists and 135 SSc experts responded. The use of high-resolution CT varied widely by country or region: 0 of 5 respondents from Australia, 2 of 6 from Canada, 28 of 47 from the United States, 45 of 57 from Europe, 4 of 5 from Asia, and 7 of 7 from Latin America.

A lack of data on how often rheumatologists order high-resolution CT for their newly diagnosed patients and absence of clinical practice guidelines prompted the survey.

The researchers also found little consensus on indications for high-resolution CT in SSc patients. Among the SSc experts who do not routinely obtain screening high-resolution CTs in their SSc patients, 81% said they would request one for dyspnea on exertion, 74% would request one for an abnormal forced vital capacity less than 80% of predicted, and 52% would request one for an abnormal diffusion capacity for carbon monoxide less than 80% predicted.

A significant limitation of the study was the low response rate, and more research is needed on the clinical impact of high-resolution CT screening for ILD in SSc patients, the researchers noted. However, the results highlight the need for a clinical practice guideline to create a more consistent approach to identifying ILD in these patients, they said.

The researchers had no financial conflicts to disclose. Dr. Bernstein was supported by a Rheumatology Research Foundation Scientist Development Award, and two of her colleagues were funded in part by the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the National Heart, Lung, and Blood Institute.

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SOURCE: Bernstein E et al. Arthritis Rheumatol. 2018 Feb 9. doi: 10.1002/art.40441.

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Preop physiotherapy training cuts risk of postop pulmonary complications

BY TERRY L. KAMPS
Frontline Medical News

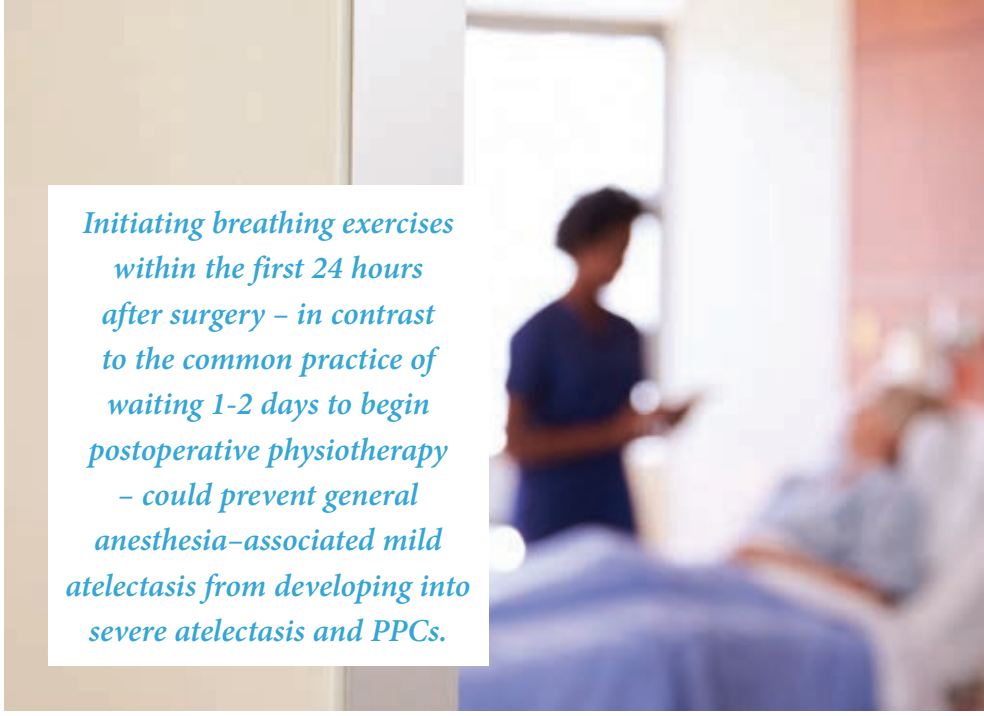
A single 30-minute coaching session with a physiotherapist within 6 weeks of major upper abdominal surgery significantly reduced postoperative pulmonary complications (PPC), according to the results of a prospective trial.

Ianthe Boden and her colleagues recruited 441 eligible adults scheduled for elective major upper abdominal surgery to participate in the prospective, multicenter, double-blinded, controlled superiority study to assess whether PPC outcomes were affected by preoperative physiotherapy. Consecutive participants were obtained from outpatient preadmission assessment clinics during June 2013 to August 2015; they were assigned randomly in a 1:1 ratio to the control (219) or intervention (222) groups. The median patient age was 68 years for the control and 63 for the intervention group, and each group was composed of 31% women.

As a component of accepted standard care, all participants in the trial were provided a booklet with written and pictorial information on occurrence of PPCs, along with prevention strategies that consisted of exercises involving early ambulation and prescribed breathing, according to Ms. Boden of Launceston (Tasmania) General Hospital, Australia, and her colleagues.

Immediately after receiving the booklets, however, participants in the intervention group were also given an added 30-minute education and training session by preoperative physiotherapists. This instruction covered factors contributing to PPC occurrence, strategies to help prevention it, and three coached repetitions of breathing exercises. Emphasis was placed on initiating prescribed breathing exercises upon regaining postoperative consciousness and continuing them every hour until the patients were fully ambulatory.

The primary outcome was evaluated by masked assessors using the Melbourne group score criteria to determine PPC incidence within 14 postoperative days or by the time of hospital discharge, whichever was sooner. Nine participants, four from the intervention and five from the control group, withdrew from the study. Of the total remaining 432 participants, 85 (20%) had a documented PPC incident, including hospital-acquired pneumonia, within the specified postoperative time frame, as reported in the BMJ.



Initiating breathing exercises within the first 24 hours after surgery – in contrast to the common practice of waiting 1-2 days to begin postoperative physiotherapy – could prevent general anesthesia–associated mild atelectasis from developing into severe atelectasis and PPCs.

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Results showed that the physiotherapy group had significantly fewer PPC occurrences (27/218, 12%) than did the control group (58/214, 27%). The calculated absolute risk reduction was 15% (*P* less than .001). Adjustment for three of the prespecified covariates (age, respiratory comorbidity, and surgical procedure) showed PPC incidence remained halved (hazard ratio, 0.48; $P = .001$) for the intervention group with a number needed to treat of 7 (95% confidence interval, 5-14).

Ms. Boden and her colleagues proposed that the timing for patients to begin breathing exercises after major open upper abdominal surgery could be critical in reducing PPC incidence. Initiating breathing exercises within the first 24 hours after surgery – in contrast to the common practice of waiting 1-2 days to begin postoperative physiotherapy – could prevent general anesthesia–associated mild atelectasis from developing into severe atelectasis and PPCs.

The authors reported that they received grants from the Clifford Craig Foundation; the University of Tasmania, Hobart, Australia; and the Waitemata District Health Board in Auckland, New Zealand.

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SOURCE: Boden I et al. BMJ. 2018. doi: 10.1136/bmj.j5916.

DMARDs may hamper pneumococcal vaccine response

BY MICHELE G. SULLIVAN
Frontline Medical News

Patients taking disease-modifying antirheumatic medications for systemic sclerosis appear to have a decreased response to pneumococcal vaccines, a Swedish study has determined.

Those not taking disease-modifying antirheumatic medications (DMARDs), however, had a normal immune response, suggesting that it's the immunomodulating medications, not the disease itself, that is affecting antibody levels, Roger Hesselstrand, MD, of Lund (Sweden) University and his colleagues reported online in Rheumatology.

"The currently recommended prime-boost vaccination strategy using a dose of PCV13 [13-valent pneumococcal conjugate vaccine] followed by a dose of PPV23 [23-valent pneumococcal polysaccharide vaccine] might be a possible way of enhancing the vaccine immunogenicity in immunosuppressed patients," the authors wrote.

The study comprised 44 subjects with systemic sclerosis, 12 of whom were taking a DMARD (mycophenolate mofetil, azathioprine, or hydroxychloroquine), and 49 healthy controls; all underwent pneumococcal vaccination. The first 13 got a single dose of PPV23 intramuscularly. PCV13 was then licensed for adults in Sweden, and the remaining 31 patients received this vaccine. The primary outcome was 6-week change from baseline in the level of pneumococcal IgG to *Streptococcus pneumoniae* serotypes 23F and 6B.

Both vaccines were safe and well-tolerated by all patients, including those taking a DMARD.

Before vaccination, antibody levels to both serotypes were similar between the groups. After vaccination, antibody levels for both serotypes increased significantly in systemic sclerosis patients not taking a DMARD and in controls. However, patients taking a DMARD mounted only an adequate response to serotype 6B.

"Compared with [patients] without DMARDs, patients [taking DMARDs] had lower postvaccination antibody levels, [lower] mean fold increase in antibody concentration, and [a lower] percentage of patients reaching putative protective antibody levels for both serotypes," the authors wrote.

There were fewer responders among those taking DMARDs, whether they received the PCV13 or the PPV23 vaccine. An increase from prevaccination antibody levels of at least twofold occurred in fewer patients taking DMARDs than did in patients not taking DMARDs and in controls, regardless of vaccine type (PPV23, 50% vs. about 55% and 50%, respectively; PCV13, about 17% vs. 57% and 100%, respectively).

"We demonstrated that the antibody response ... as well as functionality of antibodies in [systemic sclerosis] patients not receiving DMARDs was as good as in controls regardless of vaccine type," the investigators concluded. "Systemic sclerosis patients treated with DMARDs, however, had lower proportion of patients with positive antibody response, although the functionality of the antibodies was preserved."

None of the authors had conflicts of interest to disclose.

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SOURCE: Hesselstrand R et al. Rheumatology [Oxford]. 2018 Jan 8. doi: 10.1093/rheumatology/kex471.

Status asthmaticus risk increased with IV labetalol

BY KARI OAKES
Frontline Medical News

DALLAS – A maternal death occurred at Columbia University Medical Center after a patient with asthma was given intravenous labetalol, prompting a study that found an elevated risk of status asthmaticus associated with intravenous labetalol administration but not with the uterotonic carboprost.

"Overall, 71.4% of status asthmaticus cases occurred among women receiving IV labetalol," said Whitney A. Booker, MD, speaking about the findings at the meeting sponsored by the Society for Maternal-Fetal Medicine.

Dr. Booker and her colleagues used a national database to determine that the incidence of status asthmaticus in patients with asthma was almost four times higher when patients with preeclampsia were given IV labetalol: The rate was 6.5 per 1,000 patients given IV labetalol, compared with 1.7 per 1,000 for patients who received other antihypertensives.

The risk of status asthmaticus didn't reach statistical significance

KARI OAKES/FRONTLINE MEDICAL NEWS

Dr. Whitney A. Booker: "Overall, 71.4% of status asthmaticus cases occurred among women receiving IV labetalol."

when women with asthma who experienced postpartum hemorrhage were given carboprost, compared with other uterotonics (3.1 vs. 1.0 per 1,000 patients; $P = .56$).

"Some regularly used medications in obstetrics can trigger bronchospasm," said Dr. Booker; the American College of Obstetricians and Gynecologists lists both carboprost and labetalol as contraindicated for use in patients with asthma because of the potential for bronchospasm with each medication.

However, she said, data on the actual risk of bronchospasm when these medications are used in obstetric patients are limited.

The retrospective cohort study constructed by Dr. Booker and her colleagues at Columbia University Medical Center's department of obstetrics and gynecology tapped 10 years' worth of data from a large inpatient drug utilization database.

Dr. Booker, a maternal-fetal medicine fellow, said that patients were included if they were admitted for delivery and had a diagnosis of preeclampsia or postpartum hemorrhage. Of the 5.7 million hospitalizations from 2006 to 2015, 2.5% were for postpartum hemorrhage, and 4.2% for preeclampsia.

Of the patients with hemorrhage, 5,633 had a prior history of asthma, as did 12,486 of the patients with preeclampsia. In both groups, a little more than a third of patients were younger than 25 years, and about a quarter were black. Half were on Medicaid, and most were in urban areas and cared for in a teaching hospital.

The first outcome that Dr. Booker and her colleagues looked at was how practice patterns for postpartum hemorrhage varied according to whether patients had asthma; to do so, they looked at receipt of carboprost, misoprostol, and methylergonovine. A similar analysis was performed for the second outcome addressing patients with preeclampsia, in which investigators examined the use of both IV and oral labetalol, hydralazine, and nifedipine. For this and the hemorrhage outcome, the investigators performed multivariable analysis, with receipt of carboprost and IV labetalol as the outcomes of interest.

Finally, the investigators assessed the risk of status asthmaticus by comparing receipt of either carboprost (for postpartum hemorrhage) or IV labetalol (for preeclampsia) with receipt of the other medications to treat these conditions.

They found that overall 11.4% of patients with asthma and 18% of patients without asthma received carboprost to treat postpartum hemorrhage, which makes for an adjusted risk model of 0.68 (95% confidence interval, 0.62-0.74) for receipt of carboprost for patients with asthma versus those without.

However, the pattern was different for IV labetalol: 18.5% of patients with asthma and preeclampsia received labetalol, compared with 16.7% of those without asthma. After statistical adjustment, patients with asthma had a risk ratio of 0.93 (95% CI, 0.90-0.97) for receiving IV labetalol for preeclampsia.

The analysis showed that pregnant patients with asthma were less likely to be given carboprost than labetalol, although the actual risk of status asthmaticus was higher when patients with asthma received labetalol than when they received carboprost.

"Given similar theoretical risks, obstetric providers currently administer carboprost differently than labetalol. ... Obstetricians should proceed with caution prior to giving labetalol to patients with underlying asthma," said Dr. Booker.

Dr. Booker and her colleagues reported that they had no conflicts of interest.

The study was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

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SOURCE: Booker WA et al. Am J Obstet Gynecol. 2018 Jan;218:S51.

VIEW ON THE NEWS

Daniel Ouellette, MD, FCCP, comments: I teach my residents and fellows the "rule of thirds": One-third of asthma patients get worse during pregnancy; one-third get better; one-third stay the same." Asthma during pregnancy remains a challenging problem, with physicians striving to treat two complicated patients (mother and child) safely and effectively. We learn now that the use of labetalol, a beta-blocker, to treat preeclampsia in pregnant asthma patients may be associated with an increased incidence of status asthmaticus. Until we learn more about these occurrences, we should use great caution in treating pregnant asthma patients with labetalol and other beta-blockers.

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Ceftazidime-avibactam equals meropenem for nosocomial pneumonia

BY SHANNON AYMES
Frontline Medical News

Ceftazidime-avibactam was noninferior to meropenem for nosocomial pneumonia including ventilator-associated pneumonia from gram-negative organisms, results from the REPROVE trial demonstrated.

Nosocomial or hospital-acquired pneumonia is a common hospital-acquired infection associated with increased cost and mortality. Further, nosocomial pneumonia is associated with gram-negative pathogens such as *Pseudomonas aeruginosa* and Enterobacteriaceae that may carry extended-spectrum beta-lactamases and carbapenemase, thereby limiting the treatment options. However, ceftazidime-avibactam has both antipseudomonal and extended beta-lactamase coverage for multidrug-resistant gram-negative infections, and may provide an alternative to meropenem.

Antoni Torres, MD, of the University of Barcelona and his colleagues sought to compare the safety and efficacy of ceftazidime-avibactam to meropenem in patients with nosocomial and ventilator-associated pneumonia. The REPROVE study was a phase 3, double-blind, noninferiority trial performed at 136 centers in 23 countries. Patients were randomly assigned 1:1 to receive either ceftazidime-avibactam (500-2,000 mg every 8 hours) or meropenem (1,000 mg every 8 hours) with adjustment as needed for renal function.

Participants included in the study were 18-90 years of age with nosocomial pneumonia as evidenced by pneumonia 48 hours or more after admission or within 7 days after discharge from an inpatient facility. Patients with ventilator-associated pneumonia had lung infection within 48 hours of intubation and mechanical ventilation. Sputum culture and gram stains were obtained within 48 hours before randomization, and patients were excluded for evidence of gram positive–only pathogens or those not expected to respond to meropenem or ceftazidime-avibactam.

The study involved a safety population (808 patients), a clinically modified intention-to-treat population (726), and a clinically evaluable population (527). The intention-to-treat population demonstrated a predominance of *Klebsiella pneumoniae* (37%), and *Pseudomonas aeruginosa* (30%); 28% of the intention-to-treat population were identified as not susceptible to ceftazidime.

Overall, the clinically modified intention-to-treat group demonstrated a clinical cure rate of 68.8% (245/356) in the ceftazidime-avibactam and 73.0% (270/370) for the meropenem group (difference, –4.2%; 95% confidence interval, –10.8 to 2.5). The evaluable population demonstrated a clinical cure rate of 77.4% (199/257) in the ceftazidime-avibactam group and 78.1% (211/270) in the meropenem group (–0.7%; 95% CI, –7.9 to 6.4).

The all-cause mortality rate was similar between groups at the test-of-cure date and at day 28. The clinically modified intention-to-treat population demonstrated a mortality of 8.1% vs. 6.8% at the test-of-cure date and 8.4% vs. 7.3% at day 28 for ceftazidime-avibactam and meropenem, respectively.

Adverse events were noted in 75% vs. 74% of patients in the ceftazidime-avibactam groups and meropenem groups, respectively. Most adverse events were rated as mild to moderate and deemed likely unrelated to the treatment.

However, serious adverse events occurred in 19% (n = 75) in the ceftazidime-avibactam group and 13% (n = 54) in the meropenem group. Four serious adverse events were thought to be possibly related to the study drug ceftazidime-avibactam and included diarrhea, acute coronary syndrome, subacute hepatic failure, and abnormal liver function test results. The authors noted the adverse events in the trial were consistent and detected no new safety concerns for ceftazidime-avibactam.

The study was initially funded by AstraZeneca until the rights to ceftazidime-avibactam were acquired by Pfizer. Multiple authors reported financial relationships with AstraZeneca including grant funding, employment, and shareholding.

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SOURCE: Torres A et al. Lancet Infect Dis. 2017. doi: 10.1016/S1473-3099(17)30747-8.

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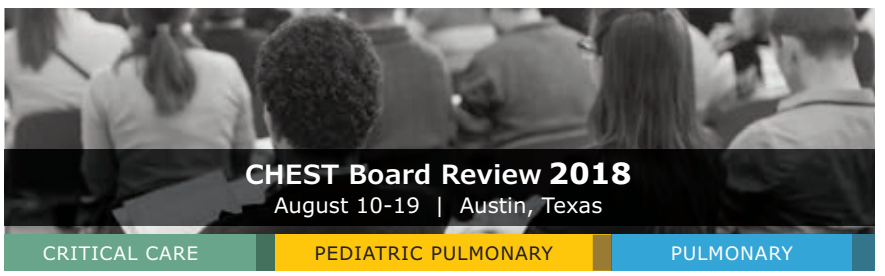

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California tops state tobacco prevention spending

BY RICHARD FRANKI
Frontline Medical News

California will spend almost as much money on tobacco prevention and smoking cessation as the other states combined in 2018, putting it closest to the spending level recommended for each state by the Centers for Disease Control and Prevention, according to a report on the effects of the 1998 tobacco settlement.

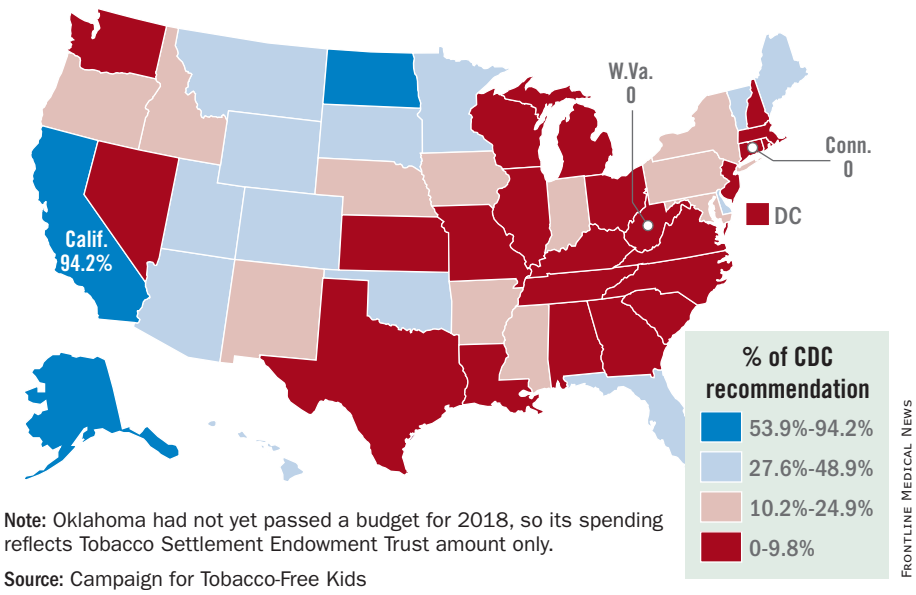
The Golden State has budgeted almost $328 million for tobacco prevention and cessation this year, which amounts to just over 45% of all states' total spending of $722 million and 94% of the CDC's recommendation of $348 million. Alaska is the only state close to that in terms of the CDC-recommended level, reaching 93% of its spending target of $10.2 million. In third place for recommended spending is North Dakota, which has budgeted $5.3 million for 2018, or 54% of its CDC target, the report said.

"Broken Promises to Our Children: A State-by-State Look at the 1998 Tobacco Settlement 19 Years Later" was released by the Campaign for Tobacco-Free Kids, American Cancer Society Cancer Action Network, American Heart Association, American Lung Association, Robert Wood Johnson Foundation, Americans for Nonsmokers' Rights, and Truth Initiative.

The report also pointed out that the $722 million the states will spend this year amounts to just 2.6% of the $27.5 billion they will collect from the 1998 tobacco settlement and tobacco taxes.

As for actual spending, Florida is second behind California with almost $69 million – 35% of its CDC-recommended level – budgeted for tobacco prevention and smoking cessation in 2018, and New York is third at just over $39 million, which is 19.4% of the CDC recommendation.

State spending on tobacco prevention for fiscal year 2018



Frontline Medical News

Note: Oklahoma had not yet passed a budget for 2018, so its spending reflects Tobacco Settlement Endowment Trust amount only.

Source: Campaign for Tobacco-Free Kids

Two states – Connecticut and West Virginia – will spend no money on such programs this year, the report noted.

The CDC has said that all states combined should be spending $3.3 billion for the year on prevention and cessation efforts, which is about 4.5 times higher than actual budgeted spending.

The report also pointed out that the $722 million the states will spend this year amounts to just 2.6% of the $27.5 billion they will collect from the 1998 tobacco settlement and tobacco taxes. By comparison, the report cited data from the Federal Trade Commission showing that the tobacco companies spent $8.9 billion on marketing in 2015.

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States judged on smoking cessation services

BY RICHARD FRANKI
Frontline Medical News

Minnesota and South Carolina are at the top of the class for access to smoking cessation services, but a new report card from the American Lung Association shows that the treatment coverage in most states earned barely passable or failing grades. In fact, 31 states received either a D (11 states) or an F (20 states) on the grading system. There were also 11 C's and 7 B's to go along with the two A's, the ALA said in "State of Tobacco Control 2018."

The cessation coverage grades are based on a 70-point total, with a maximum of 40 points awarded for a state's Medicaid coverage (smoking rates are much higher and incomes lower among Medicaid enrollees than the general population), 20 points for the investment per smoker in the state's phone quitline, and 10 points for state employee health plan coverage.

Minnesota received 66 points and South Carolina earned 63 after a 5-point deduction for not expanding Medicaid up to Affordable Care Act standards. The highest-finishing states with B's were Vermont with 62 points and Maine with 61, and the lowest total score was the 23 points earned by Virginia and Washington, although Washington's grade did not include the state employee category since the state did not provide data on its plan, the ALA noted.

The Department of Health & Human Services recommends that tobacco cessation coverage include the use of five nicotine-replacement therapies, bupropion and vanenicline, and three types of counseling, the report said.

The Department of Health & Human Services recommends that tobacco cessation coverage include the use of five nicotine-replacement therapies (gum, patch, lozenge, nasal spray, inhaler), bupropion and varenicline (nonnicotine medications), and three types of counseling (individual, group, and phone), the report said.

"It's imperative that all state Medicaid programs cover a comprehensive tobacco cessation benefit, with no barriers, to help smokers quit, including all seven [Food and Drug Administration]–approved medications and three forms of counseling for Medicaid enrollees. In 2017, only Kentucky, Missouri, and South Carolina provided this coverage," wrote Harold P. Wimmer, national president and CEO of the ALA.

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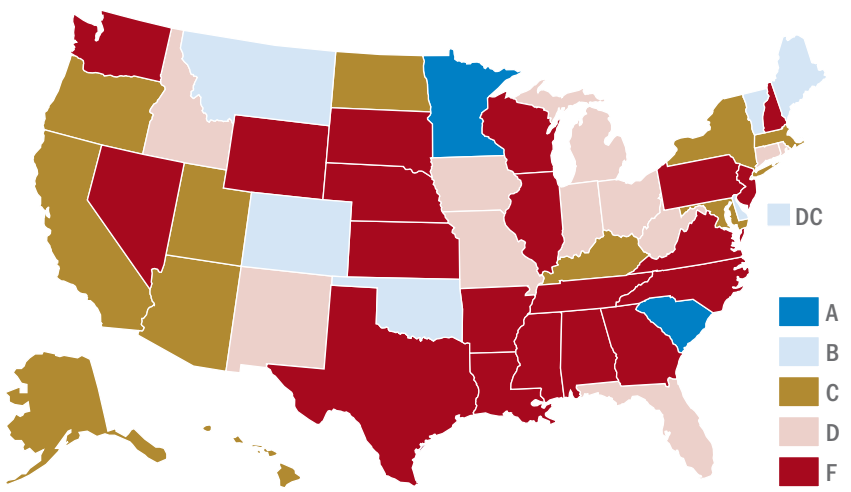
States' access to smoking cessation services graded



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Note: The grading system covers three areas: Medicaid coverage, state employee health plan coverage, and investment per smoker each state makes in its phone quitline.

Source: American Lung Association

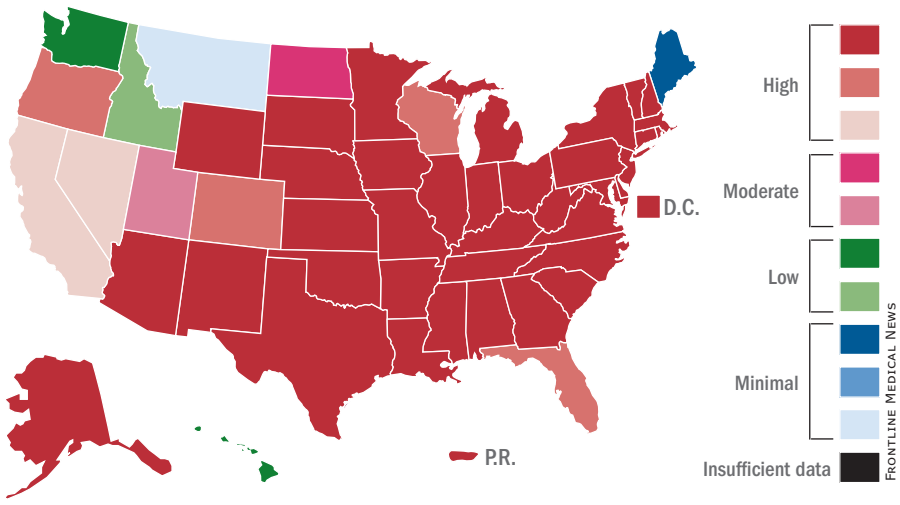
Flu increase may be slowing

BY RICHARD FRANKI
Frontline Medical News

A bit of revisionist history has outpatient influenza activity at a lower level than was reported last week, even though it hasn't dropped.

The proportion of outpatient visits for influenza-like illness (ILI) for the week ending Feb. 10 was 7.5%, according to the Centers for Disease Control. That is lower than the 7.7% previously reported for the week ending Feb. 3, which would seem to be a drop, but the CDC also has revised that earlier number to 7.5%, so there is no change. (This is not the first time an earlier ILI level has been retroactively lowered: The figure reported for the week ending Jan. 13 was revised in the following report from 6.3% down to 6.0%.)

Influenza-like illness activity level, week ending Feb. 10, 2018



Note: Based on data from the U.S. Outpatient Influenza-like Illness Surveillance Network.
Source: Centers for Disease Control and Prevention

These two consecutive 7.5%'s mean that ILI activity for the 2017-2018 season has not quite matched that of the pandemic in 2009, which hit 7.7% and also suggests that outpatient visits may have finally peaked. That is supported by a slight reduction in the number of states at the highest level of ILI activity, which went from 41 down to 39, although the number in the "high" range (8-10) on the CDC's 1-10 scale went up from 44 to 45, according to data from the CDC's Outpatient Influenza-like Illness Surveillance Network.

Hospital visits, however, continue to rise at record levels. The cumulative rate for the week ending Feb. 10 was 67.9 visits per 100,000 population, which is higher than the same week for the 2014-2015 (52.9 per 100,000) when flu hospitalizations for the season hit a high of 710,000. Flu-related pediatric deaths also went up, with 22 new reports; this brings the total to 84 for the 2017-2018 season.

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New device cuts postoperative pulmonary complications

BY ANDREW D. BOWSER
Frontline Medical News

OLLEGA/THINKSTOCK

SAN ANTONIO – A device that combines lung expansion, mucus clearance, and aerosol delivery appears to reduce postoperative pulmonary complications, according to results of a nonrandomized study including high-risk patients undergoing elective surgical procedures.

"For certain types of surgical procedures, this therapy (MetaNeb, Hill-Rom) may provide a benefit for high-risk patients in terms of reducing their pulmonary complications and their hospital stay," said Toan Huynh, MD, lead investigator and director of trauma research at Carolinas HealthCare System, Charlotte, N.C., at the Critical Care Congress sponsored by the Society for Critical Care Medicine.

Currently, aggressive management of high-risk patients with strategies such as optimal analgesia, early ambulation, secretion mobilization, and lung expansion are used to try to reduce the incidence of postoperative pulmonary complications, noted Dr. Huynh, in an interview.

In this study, Dr. Huynh and his colleagues from the University of Pennsylvania, Philadelphia, and the Lahey Hospital & Medical Center, Burlington, Mass., sought to evaluate the efficacy of the MetaNeb system, which delivers continuous high-frequency oscillation, continuous positive expiratory pressure, and in-line aerosol flow in one combined unit. To estimate usual postoperative pulmonary complication rates, they first queried CPT and ICD-9-CM codes to identify a total of 210 patients who had undergone thoracic, upper-abdominal, or aortic open surgical procedures. Then, in the second stage of the study, the investigators prospectively enrolled 209 subjects who underwent those types of surgery with the MetaNeb system in addition to a standard postoperative respiratory regimen. All patients were high risk as defined by having either an American Society of Anesthesiologists classification of at least 3 or an ASA classification of 2 along with one or more comorbidities, such as COPD or recent smoking history.

Among the patients managed with MetaNeb, 33 (15.8%) experienced one or more pulmonary complications, compared with 48 (22.9%) in the retrospective cohort ($P = 0.06$). For intubated patients, at least one complication was seen in 22 patients (36.7%) in the MetaNeb group, compared with 37 (69.8%) in the comparison group (P less than .05). Time on mechanical ventilation was 8.5 hours in the MetaNeb group versus 23.7 hours in the comparison group (P less than .05).

Use of the device was also associated with decreased length of hospital stay, but the difference between lengths of stay was not statistically significant. Hospital length of stay was 6.8 days in the MetaNeb versus 8.4 days in the comparison groups.

"In the current day and age of value-based health care, I think any kind of reduction in expenditure related to health care costs would be compelling for clinicians," Dr. Huynh said in the interview.

Further study may be needed to better define the role of the combined modality system in clinical practice, according to Dr. Huynh.

"This is sort of a 'before and after' nonrandomized trial," Dr. Huynh explained. "I think, ideally, if we can do a truly controlled, randomized trial, that will be much more powerful."

The study was sponsored by Hill-Rom, which manufactures the device under study. Dr. Huynh said he and coinvestigators had no financial conflicts related to the research.

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SOURCE: Huynh T et al. Critical Care Congress, Abstract 17.

Birth cohort affected 2015-2016 flu vaccine

BY BIANCA NOGRADY
Frontline Medical News

The influenza vaccine introduced in 2009 showed reduced effectiveness during the 2015-2016 influenza season, but only in adults born between 1958 and 1979, according to an analysis published online in the Journal of Infectious Diseases.

Using the Influenza Vaccine Effectiveness Network, researchers analyzed data from 2,115 patients with medically attended acute respiratory illness who tested positive for A(H1N1)pdm09 influenza virus, and 14,696 patients who tested negative for the influenza virus, from 2010-2011 to 2015-2016 (excluding the 2014-2015 influenza season).

Overall, 48% of the influenza virus–negative patients and 28% of the virus-positive patients had received at least one dose of the seasonal inactivated influenza vaccine more than 2 weeks before they fell ill.

However, the vaccine, which was based on the A/California/07/2009 strain of the A(H1N1) pdm09 virus, was only 47% effective during the 2015-2016 season, compared with 61% effectiveness during the 2010-2011 season through to the 2013-2014 season.

When researchers looked at vaccine effectiveness by birth cohort, they found that one particular cohort – individuals born between 1958 and 1979 – showed a significantly reduced vaccine effectiveness (22%) during the 2015-2016 season. By comparison, vaccine effectiveness in this cohort was 61% during the 2010-2013 seasons, and 56% during the 2013-2014 season.

When this birth cohort was excluded from analysis of the 2015-2016 season, the overall vaccine effectiveness for that season was 61%.

While the vaccine was based on an early reference strain of A(H1N1)pdm09, the virus itself later acquired mutations in the hemagglutinin gene, leading to the emergence of new genetic clades, including 6B, which dominated in the 2013-2014 influenza season, and 6B.1, which dominated in 2015-2016.

"Limited serologic data suggest that some adults born during 1958-1979 (age range in 2015-2016, 36-57 years) have decreased antibody titers against A(H1N1)pdm09 group 6B and 6B.1 viruses," wrote Brendan Flannery, PhD, from the Centers for Disease Control and Prevention, and his coauthors.

They suggested that individuals in this cohort may have been immunologically primed with A/USSR/90/1977-like viruses, which were the first group of A(H1N1) viruses that this cohort would have been exposed to. A(H1N1) strains didn't circulate between 1958 and 1977. Vaccination with A(H1N1)pdm09 viruses may have induced antibodies against shared antigenic components found on early versions of A(H1N1)pdm09.

"Limited serologic data suggest that some adults born during 1958-1979 (age range in 2015-2016, 36-57 years) have decreased antibody titers against A(H1N1) pdm09 group 6B and 6B.1 viruses."

If these shared antigenic epitopes were then altered in the later 6B and 6B.1 viruses, that might account for decreased antibody titers in this age group.

"Replacement of the A/California/07/2009 (H1N1)pdm09 vaccine reference strain with A/Michigan/45/2015 (group 6B.1) should lead to improved [vaccine effectiveness] against circulating A(H1N1)pdm09 viruses," the researchers noted.

The study was supported by the Centers for Disease Control and Prevention, the National Institutes of Health, and the National Center for Advancing Translational Sciences. Eight authors declared funding, grants, and consultancies with the pharmaceutical industry, with five also declaring funding from the CDC.

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SOURCE: Flannery B et al. J Infect Dis. 2018 Jan 18. doi: 10.1093/infdis/jix634.

VIEW ON THE NEWS

Early influenza encounters could influence vaccine response

This study proposes that influenza virus strains encountered early in life focus the immune response to later infection or vaccination on shared epitopes between the early and later strains. Supporting this hypothesis is evidence from other studies showing that 60% of the serological response to inactivated influenza vaccines is the result of boosting pre-existing antibodies, rather than the creation of new, vaccine-induced antibodies.

However there are also some flaws to this argument, and we should be careful to avoid confirmation bias. For example, the reduction in effectiveness of vaccines against A(H1N1) has been observed in North America, where this study is located, but to a lesser extent in studies conducted in other regions. Reductions in vaccine effectiveness have also been observed in other birth cohorts and during other influenza seasons.

That aside, accumulating evidence suggests that the vaccine strain be updated from A/California/7/2009 to A/Michigan/45/2015 (a clade 6B.1 strain) for the 2016-2017 influenza seasons.

Allen C. Cheng, PhD, is from the School of Public Health and Preventive Medicine at Monash University, Melbourne, and Kanta Subbarao, MBBS, is from the World Health Organization Collaborating Centre for Reference and Research on Influenza and the Peter Doherty Institute for Infection and Immunity, Australia. These comments are taken from an accompanying editorial (J Infect Dis. 2018, Jan 18. doi: 10.1093/infdis/jix635). *The authors declared support from the Australian Department of Health and the Australian National Health and Medical Research Council. No conflicts of interest were declared.*

Drug combo indicated for bacterial pneumonia

BY CHRISTOPHER PALMER
Frontline Medical News

The Food and Drug Administration has approved expanding the indication for the drug combination of ceftazidime and avibactam (Avycaz) to include hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) in adults.

Specifically, the approved indication is for infections caused by certain gram-negative bacteria – some of which are increasingly resistant to available antibiotics – including, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Escherichia coli*, *Serratia marcescens*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Haemophilus influenzae*.

There have not been new treatment options for HABP/VABP caused by Gram-negative bacteria in more than 15 years, according to Allergan, the drug's manufacturer.

The approval of the expanded indication was based on data from the phase 3, multinational, double-blind REPROVE trial. The study showed that ceftazidime/avibactam was noninferior to meropenem with respect to 28-day all-cause mortality.

This is the third approved indication for ceftazidime/avibactam; the other two indications are for complicated intra-abdominal infections (in combination with metronidazole) and for complicated urinary tract infections.

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Turning Up the Heat on ICU Burnout

BY CURTIS N. SESSLER, MD, FCCP

The work of critical care clinicians can create a perfect storm for emotional exhaustion, depersonalization, and reduced self-efficacy – widely known as burnout. Burnout is occurring in record numbers among physicians in general – more than twice as frequently as for non-health-care workers – and intensivists top the chart. Clinicians from all specialties in medicine today experience the frustrations of workplace chaos and loss of control, displacement of meaningful work with menial work, and ever increasing documentation requirements and electronic health record challenges – all contributing to burnout. Intensivists and other ICU professionals, such as advanced practice providers and nurses, however, experience the added challenge of working in a highly stressful environment characterized by fast-paced high-stakes decision making, long and irregular hours, and end-of-life scenarios often clouded by moral distress. These and other drivers contribute to high rates of burnout.

DR. CURTIS N. SESSLER

Being burned out takes its toll on health-care workers, contributing to psychological and physical manifestations, alcohol or substance abuse, posttraumatic stress disorder, and even suicidal ideation. Additionally, burnout carries important negative consequences for the organization and directly to the patient, including higher rates of employee turnover, lower quality of work, more medical errors, and reduced patient satisfaction. Unfortunately, burnout rates continue to rise with alarming speed.

Fortunately, there is increasing attention paid to the magnitude and potential impact of burnout, compelling important organizations to highlight the problem and assist clinicians in combating burnout and its consequences. For example, the National Academy of Medicine (NAM) has convened an Action Collaborative on Clinician Well-Being and Resilience and invited more than 100 organizations to publish their statement of commitment to improve clinician well-being and reduce clinician burnout (https://nam.edu/initiatives/clinician-resilience-and-well-being/). The American Medical Association (AMA) has developed modules and tools to assist clinicians and administrators in taking important steps to prevent burnout (https://www.stepsforward.org/modules/physician-burnout).

CHEST has been an active participant in addressing burnout in ICU professionals, including in an important partnership with the American Association of Critical-Care Nurses (AACN), the American Thoracic Society (ATS), and the Society of Critical Care Medicine (SCCM) - the Critical Care Societies Collaborative (CCSC). The CCSC, whose members include greater than 150,000 critical care professionals in the United States, has established a principle goal of mitigating ICU burnout (#StopICUBurnout). One of the first CCSC efforts was to publish a white paper simultaneously in all four journals of the CCSC professional societies that provides the rationale and direction for a "call for action" to tackle ICU burnout (Moss M, Good VS, Gozal D, Kleinpell R, Sessler CN. Burnout syndrome in critical care health care professionals: A call for action. *Chest.* 2016;150[1]:17). Recently, the CCSC sponsored a National Summit on the Prevention and Management of Burnout in the ICU (http://ccsconline.org/optimizing-the-workforce/burnout). Fifty-five invited participants brought wide ranging expertise and substantial enthusiasm to the task of deconstructing ICU burnout and identifying knowledge gaps and future directions. Areas of focused discussion included factors influencing burnout, identifying individuals with burnout, the value of organizational and individual interventions to prevent and manage burnout, and translation of these discussions into a research agenda. *CHEST* and the CCSC are committed to the goals of enhancing clinician well-being and eliminating burnout in the ICU.

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$25,000 can help fund research investigating the factors that contribute to racial disparities in early palliative care among elderly patients with lung cancer.

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Get Ready for CHEST 2018 in San Antonio

Have you been thinking about how great of a time you had at CHEST 2017? Or, perhaps you weren't able to make it to CHEST 2017 and are looking forward to attending CHEST 2018? Well, we'd be happy to have you attend the annual meeting in sunny San Antonio, Texas, this fall. CHEST 2018 will occur earlier this year, from October 6-10, and we've got a few ways you can get involved leading up to the meeting.

CHEST 2018 Moderators

If you do not have original research to share, but believe you are qualified to moderate sessions, we have an opportunity for you! Moderating will take place on-site in San Antonio, and moderators will be recognized in the CHEST 2018 program and will receive a reduced registration rate to the meeting. See chestmeeting.chestnet.org.

CHEST Challenge 2018

Are you a US-based CHEST fellow-in-training? Compete with other programs across the country in CHEST Challenge 2018 for honor and prizes! The first round of the competition this year will consist of two parts; in addition to the traditional online quiz, there will be a number of social media challenges. The aggregate score for both of these components will be used to identify the top three-scoring teams. These top three teams will then be invited to send three fellows each to the CHEST Challenge Championship, a Jeopardy-style game show that takes place live during the CHEST Annual Meeting. http://www.chestnet.org/Hidden-Pages/CHEST-Challenge-US

CHEST Foundation Grants

We have had many talented and passionate people win our CHEST Foundation grants in research and community service. Each year, the CHEST Foundation offers grants to worthy research candidates, generous community service volunteers, and distinguished scholars in a field of expertise. Nearly 800 recipients worldwide have received more than $10 million in support and recognition of outstanding contributions to chest medicine.

How are you helping to champion lung health? The CHEST Foundation is accepting grant applications **February 1 through April 9, 2018,** in the following areas:

- CHEST Foundation Research Grant in **Lung Cancer** – $50,000 - $100,000 2-year grant*
- CHEST Foundation Research Grant in **Asthma** – $15,000 - $30,000 1-year grant*
- CHEST Foundation Research Grant in **Pulmonary Arterial Hypertension** – $25,000 - $50,000 1-year grant*
- CHEST Foundation and the **Alpha-1 Foundation Research Grant in Alpha-1 Antitrypsin Deficiency** – $25,000 - $50,000 1-year grant*
- CHEST Foundation Research Grant in **Pulmonary Fibrosis** – $25,000 - $50,000 1-year grant*
- CHEST Foundation Research Grant in **Chronic Obstructive Pulmonary Disease** – $30,000 1-year grant (multiple recipients selected)
- CHEST Foundation Research Grant in **Venous Thromboembolism** – $15,000 - $30,000 1-year grant*
- CHEST Foundation Research Grant in **Nontuberculous Mycobacteria Disease** – $25,000 - $50,000 1-year grant*
- CHEST Foundation Research Grant in **Women's Lung Health** – $10,000 1-year grant
- CHEST Foundation Research Grant in **Cystic Fibrosis** – $30,000 1-year grant
- The Eli Lilly and Company **Distinguished Scholar** in Critical Care Medicine – $150,000 over 3 years
- CHEST Foundation **Community Service** Grant Honoring D. Robert McCaffree, MD, Master FCCP – $2,500- $15,000 1-year grant*

**Amount contingent on funding.*

Learn more on how to apply now at chestfoundation.org/apply.

Things Happening in April

Don't forget to look out for CHEST 2018 registration, **opening April 5**. And, if you missed the first round of abstract submissions, submissions for late-breaking abstracts will open April 30. Stay updated on all things CHEST 2018 at chestmeeting.chestnet.org.

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How will you prep for your 2018 board exams? Let CHEST help you prepare live and in-person for next year's pulmonary, critical care, and pediatric pulmonary exams with our comprehensive review courses.

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The 2018 lineup of CHEST live learning courses features three new additions and one past favorite. Continue to build your skills with the most relevant, hands-on chest education designed for the whole critical care team. We hope to see you next year at the CHEST Innovation, Simulation, and Training Center.

Lung Cancer: Physiologic Assessment and Optimization Prior to Therapy - A Multidisciplinary Course
July 13-15

Advanced Diagnostic and Therapeutic Bronchoscopy
August 4-5

Venovenous ECMO for Respiratory Failure
December 7-9

And back by popular demand:
Advanced Clinical Training in Pulmonary Function Testing
April 7-8

Complete Details
livelearning.chestnet.org

NAMDRC UPDATE

Collaboration: Now More Than Ever

BY RUSSEL ACEVEDO, MD, FCCP, AND GARRY KAUFFMAN, RRT

Ongoing hospital mergers, acquisitions, and closings demonstrate that reimbursement maximization and cost reduction are the twin sisters of health-care system reform. This focus is not going to change in the foreseeable future, as most experts now view "health system reform" as "health financing reform."

Reports document that more than 50% of acute care hospitals in the United States experienced negative operating margins for the federal fiscal year ending September 30, 2017. Equally alarming is the increasing number of organizations either reducing or eliminating the roles of medical directors for clinical departments. Hospital and health system executives are increasingly engaging external consultants to find ways to decrease operating costs, with the caveat of maintaining or improving quality, safety, and patient satisfaction and engagement.

Given these cost reduction pressures, what can respiratory therapy medical directors and administrative directors do to ensure that quality and safety are ensured?

We believe that quality and safety can be maintained and improved in this bottom-line-focused environment if we collaborate with stakeholders and communicate the value of respiratory care services. Following are some examples of how to reinvigorate this collaboration. The list is far from complete, but we believe it is a good starting point for making a significant difference.

Science

We recognize that much of our practice is based on levels of evidence, and we must use this evidence as a basis for our services.

In talking and working with RT administrative directors across the country, we continue to see non-value-added "treatments" being provided, such as incentive spirometry and aerosolized acetylcysteine. Not only is this a waste of resources, but, because of it, our clinical RTs are not providing therapy.

One of the best opportunities to decrease cost is to eliminate waste. These services must be eliminated. For those patients who require secretion clearance/lung expansion, we can provide evidence-based services such as oscillating positive expiratory pressure.

Protocols

Respiratory care protocols have been around for decades, but surveys indicate that only half of all RT departments utilize them. Under the guidance of NAMDRC, the AARC has been educating RTs to transition from "treatments" to evidence-based protocols. Various barriers remain, and our challenge remains to implement proven care plans in every department.

Quality Assurance

The health-care industry made the transition from "Quality Control" to "Quality Assurance" several decades ago. However, many RT administrative directors lack the knowledge and/or resources necessary to create a comprehensive QA program, much less participate in clinical research. We suggest creating a standardized model to be adopted by RT departments across the country that would measure and communicate the value of respiratory care services.

Productivity/Staffing

An area where consultants and executives often focus their cost-saving efforts is staffing. Given that 50% to 60% of operating costs are personnel, this is to be expected.

Many organizations, however, are using the wrong metrics—such as procedures, CPT codes , and billables—to project staffing FTEs. Physicians and RTs understand that these metrics are not useful and must convince consultants and executives of this. The AARC Uniform Reporting Manual, which is currently being updated, is the best guide for determining appropriate staffing.

Education

Another common step in cost control has been the significant reduction or total elimination of education budgets.

During the past 5 years, RT leaders attending the AARC Summer Forum have been polled regarding whether they received financial assistance to attend the Management Section program. Sadly, the number attending on their own dime far surpasses those receiving financial assistance.

Additionally, the RT profession is witnessing more department-based education, which, in some cases, is not education at all, but marketing, cleverly packaged in the form of CEUs.

We fully understand these changes and recognize why they have occurred. However, we suggest the need to work together to differentiate marketing from education and ensure that clinical staff receive what is needed to ensure quality care.

It is vital for us to educate our physician leaders and pulmonary and critical care fellows on the science of respiratory care. There is a significant knowledge gap, and we have a great opportunity to improve the training of fellows. It is difficult to attract active medical directors if they don't understand the science. We believe NAMDRC can play an important role by addressing these knowledge deficits.

Catching Up With Our Past CHEST Presidents

Where are they now? What have they been up to? CHEST's Past Presidents each forged the way for the many successes of the American College of Chest Physicians, leading to enhanced patient care around the globe. Their outstanding leadership and vision are evidenced today in many of CHEST's strategic initiatives. Let's check in with W. Michael Alberts.

W. MICHAEL ALBERTS, MD, MBA, MASTER FCCP
President 2005 - 2006

My year at the helm began in Montreal in 2005 and ended in Salt Lake City in 2006. The year was a blur and seemed to fly by. The inauguration was very special as my entire immediate family made the effort to attend. It was the final time that my father was able to travel. Travel was definitely one of the highlights of my Presidential year. My wife, Debra, and I made many lasting friendships and very special memories while on the road for the College.

Looking back, it is hard to believe that I have been with the University of South Florida since 1983. I came to Tampa directly from my Pulmonary and Critical Care Fellowship in San Diego. After 16 years attending at the Tampa General Hospital and the James A. Haley VA, I was named the Chief Medical Officer at the Moffitt Cancer Center in 1999. In 2015, I stepped down from that position and have been serving as the Medical Director of Moffitt's satellite clinical location since that time. I no longer do in-patient rounding, which is a major boon to work-life balance. In addition to administrative duties , however, I continue to see outpatients two half-days a week.

At the risk of sounding like a "Christmas letter," let me update you on my family. Now that my wife's father is no longer able, Debra serves as the comptroller for several family businesses. I am not sure how, but she finds time to play tennis for several teams. My son Michael recently moved to Boston from Dallas. In Texas, he was working for an investment firm focused on health care. In Boston, he manages the business development group for Shields Health Solutions. My daughter Katie is a mergers, acquisitions, and securities attorney here in Tampa, and her husband Andy is a real estate transactions attorney. We are all looking forward to the arrival of Clara Grace Peluso in June. She will be Katie and Andy's first child and Debra and my first grandchild.

In our "abundant free time," Debra and I enjoy spending time at our place on Sand Key near Clearwater Beach. When possible, we enjoy traveling and have developed our "bucket list."

Dr. Alberts and son Michael at the 2017 Masters Tournament in Augusta, Georgia.

I look back at 2005-2006 with nothing but fondness. Serving as President of the College was both intellectually and personally fulfilling. It was certainly the highlight of my career.

CHEST NetWorks

Hurricane Maria, Bloodstream Infections, Lung Cancer in Women

Disaster Response

A Natural Disaster Creates Nationwide Threat

Hurricane Maria devastated Puerto Rico in late September 2017, and the lessons learned endure as the storm exposed the vulnerability of an increasingly interconnected and fragile medical community across the continental United States. According to the US Food and Drug Administration (FDA), Puerto Rico manufactures more drug products than any US state and just under 10% of all drugs consumed by Americans, some of which do not have therapeutic alternatives. In addition, certain medical devices are only produced in Puerto Rico. The humanitarian crisis caused by Hurricane Maria consequently created critical medication and medical device shortages across the United States (FDA. https://www.fda.gov/NewsEvents/. Accessed Feb 01, 2018).

The disruption and disorganization caused by Hurricane Maria was perhaps best exemplified by the resultant shortage of small-volume 0.9% saline injection bags, which coincided with a particularly bad flu season. The FDA temporarily allowed import of saline bags from outside the United States while concurrently expediting the approval of IV solutions from new manufacturers. The American Society for Health-System Pharmacists (ASHP), meanwhile, contributed guidance on managing fluid shortages (ASHP. https://www.ashp.org/Drug-Shortages/. Accessed Feb 01, 2018).

DR. MADAR

Hurricane Maria was a wake-up call for medical professionals across the United States to modernize institutional procedures and to develop contingency plans to deal with medication shortages, particularly IV fluids, since this is a recurring problem across the United States since 2014. Ultimately, the goal of health-care providers across the United States is to manage natural catastrophes, however distant, by effectively planning for and adapting to medical product shortages to ensure patient care is not interrupted and that critical shortages remain invisible to patients themselves.

Cristian Madar, MD
Steering Committee Member

Practice Operations

Are All Regulations Well Thought Out? Point of View!

Current medicine is complex, with patients presenting in the ICU with multiorgan dysfunction. The art and science of medicine is being replaced by protocolized medicine. To help streamline the care, societies and colleges are coming up with guidelines. The guideline, though, changes from year to year what has been practiced in the past has been obsolete, and what is current may not hold true in the future. With in-

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regulation resulted in sensitizing the cells to epidermal growth factor receptor-tyrosine kinase inhibitors and may result in reversing EGFR-TK resistance (Fu et al. *Oncol Rep.* 2018;39[3]:1313).

The presence of progesterone receptors is associated with longer survival in NSCLC, and treatment with progesterone has been shown to induce apoptosis and inhibit migration and invasion of lung cancer cell lines (Ishibashi et al. *Cancer Res.* 2005;65[14]:6450). Women over the age of 60 were found to have significant survival benefit when compared with both men and younger women (Wakelee et al. *J Thoracic Oncol.* 2007b; 2:S570), whereas a worse survival and earlier age of occurrence of lung cancer was associated with the exposure to HRT (Ganti et al. *J Clin Oncol.* 2006;24[1]:59).

The future of hormone receptor targets in lung cancer may provide new therapeutic options for patients with lung adenocarcinoma, especially those with acquired resistance to the EGFR antagonists (Hsu et al. *Int J Mol Sci.* 2017; 18[8] pii: E1713. doi: 10.3390/ijms18081713).

Fidaa Shaib, MD, FCCP
Steering Committee Member
Ali Jiwani, MD
NetWork Member

This Month in the Journal *CHEST*®

Editor's Picks

BY RICHARD S. IRWIN, MD, MASTER FCCP
Editor in Chief, CHEST®

ORIGINAL RESEARCH

Community-Acquired Pneumonia Visualized on CT Scans but Not Chest Radiographs: Pathogens, Severity, and Clinical Outcomes. By Dr. C. P. Upchurch, et al.

Reduced Risk of Acute Exacerbation of COPD After Bariatric Surgery: A Self-Controlled Case Series Study. By Dr. T. Goto, et al.

COMMENTARY

CHEST: Home of the Clinician-Educator. By Dr. W. F. Kelly and Dr. A. S. Niven, on behalf of the CHEST Education Committee.

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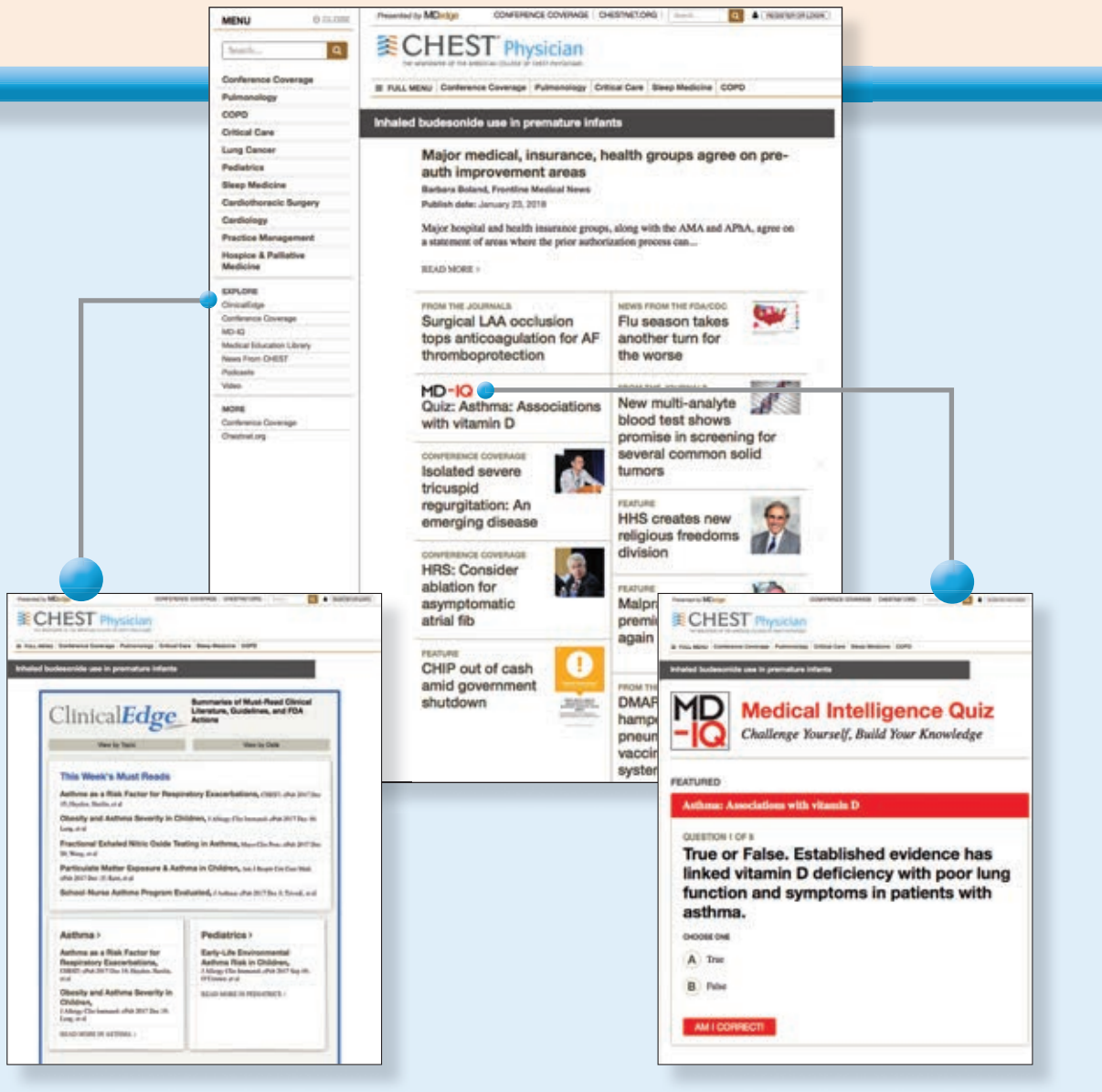

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1 Sterling, K. "Long-term Results of the OPTALYSE PE trial" as presented at the International Symposium on Endovascular Therapy (ISET) meeting, Hollywood, FL Feb 2018

2 Piazza, G., et al., A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism: the Seattle II study." *Journal of the American College of Cardiology: Cardiovascular Interventions* 2015; 8: 1382-92.

3 Tapson, et al, "Optimum Duration and Dose of r-tPA with the Acoustic Pulse Thrombolysis Procedure for Submassive Pulmonary Embolism: OPTALYSE PE," American Thoracic Society (ATS) Meeting, Washington, DC, May 2017.

The EkoSonic™ Endovascular System is not available for sale in Canada.

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