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BRUCE JANCIN/FRONTLINE MEDICAL NEWS

Systemic inflammatory response syndrome was associated with a 2.5-fold increased risk of thrombosis, said Dr. Jacques Donzé.

Even mild preop sepsis boosts postop clot risk

BY BRUCE JANCIN
Frontline Medical News

WASHINGTON – Preoperative sepsis proved to be an important independent risk factor for both arterial and venous thrombosis during or after surgery in an analysis of nearly 1.75 million U.S. surgical procedures.

The take-home message here is that the risk-benefit assessment of surgical procedures should take into account the presence of sepsis. And if the surgery can't be delayed, prophylaxis against arterial as well as venous thrombosis should be employed, Dr. Jacques Donzé said at the annual meeting of the American College of Cardiology.

Another key finding in this study was that the risk of postoperative thrombosis varied according to the severity of preoperative sepsis. Even the early form of sepsis known as systemic inflammatory response syndrome, or SIRS, was associated with a 2.5-fold increased risk.

"Include even early signs of sepsis as a risk factor," urged Dr. Donzé of Brigham and Women's Hospital, Boston.

Also, preoperative sepsis was a risk factor for postoperative thrombosis in connection with outpatient elective surgery as well as inpatient operations, he added.

Dr. Donzé presented an

See **Sepsis** • *page 18*

Some providers quicker to tube feed end-of-life elderly

Education could cut poor interventions.

BY MICHELE G. SULLIVAN
Frontline Medical News

Subspecialists who care for dementia patients near the end of life are far more likely to introduce a feeding tube than hospitalists who follow such patients.

Compared with nonhospital generalists, hospitalists were 22% less likely to tube feed hospitalized nursing-home residents – and even less likely to tube feed patients who were the most severely impaired (35%). In contrast, subspecialists were five times more likely to insert a tube. When a mixed group of physicians was on the case, rates were even higher, with a 9-fold increase overall and a 9.5-fold increase for severely demented patients.

The findings clearly illustrate that many physicians could benefit from some education about the most appropriate interventions when patients near the end of life enter a hospital, Dr. Joan Teno and her associates reported in the April issue of Health Affairs (2014;33:675-82).

"It may be that subspecialists do not have adequate knowledge about the risks and benefits of using feeding tubes in people

See **Intervention** • *page 26*

INSIDE

So you're being sued: What to do first

BY ALICIA GALLEGOS
Frontline Medical News

Receiving notice that a patient is suing can spark a range of emotions in physicians, including fear, anger, hurt, and helplessness. But litigation experts stress that after a filing, physicians must rein in their feelings and focus on immediate next steps – crucial actions that can significantly impact the suit and its outcome.

"Doctors have two reactions to getting sued – either they're very sad or they're very angry," said Steven Fitzer, a medical liability defense attorney at Fitzer, Leighton & Fitzer, P.S., in Tacoma, Wash., and former chair of the Washington State Bar Association Litigation Section. "Relaxing and composing yourself are

See **Malpractice** • *page 22*

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Off-label use of novel anticoagulants accelerates

BY BRUCE JANCIN
Frontline Medical News

WASHINGTON – The off-label use of novel oral anticoagulants for stroke prevention in patients with valvular atrial fibrillation has climbed steeply since the drugs reached the marketplace, mirroring the medications' rapid adoption for the approved indication of preventing strokes in nonvalvular AF, according to Dr. Sandeep Mahrendra Jani.

An analysis of 190,227 nonvalvular atrial fibrillation (NVAF) patients in 95 practices participating in the American College of Cardiology's National Cardiovascular Data Registry – PINNACLE Registry – showed that during the first quarter of 2011, just 4.8% were on dabigatran, the sole novel oral anticoagulant then available. By the fourth quarter of 2012, however, 14.9% of NVAF patients were on a novel oral anticoagulant, either dabigatran or the subsequently approved rivaroxiban, he reported at the annual meeting of the ACC.

Similarly, among 2,142 registry participants with valvular atrial fibrillation (AF), the use of any novel oral anticoagulant shot up from 2.7% in the first quarter of 2011 to 13.8% in the fourth quarter of 2012, noted Dr. Jani of Medstar Washington (D.C.) Hospital Center.

During this time – prior to the arrival of apixiban on the market – the use of warfarin for stroke prevention in patients with NVAF declined from 47.9% to 44.3%. Among patients with valvular atrial fibrillation, the prevalence of warfarin therapy fell from 65.8% in the first quarter of 2011 to 60.1% in fourth quarter 2012.

During the first quarter of 2011, 51.2% of all patients with NVAF and 66.4% with valvular AF were on any oral anticoagulant. By fourth quarter 2012, these rates had increased to 56.9% and 66.8%, respectively.

The use of dabigatran in patients with valvular AF took a hit in late 2012 in response to the premature halt of the RE-ALIGN (Dabigatran Etexilate in Patients With Mechanical Heart Valves) trial, followed by the Food and Drug Administration's warning against using dabigatran in patients with mechanical heart valves. Dabigatran was used by 2.7% of valvular AF patients in the first quarter of 2011, rising steadily to 12.1% by the third quarter of 2012, then plunging to just 1.4% in the year's final quarter.

Further studies are a priority, Dr. Jani said.

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VITALS

Key clinical point: Off-label use of novel anticoagulants is growing.

Major finding: By the fourth quarter of 2012, about 15% of patients with nonvalvular AF and about 14% of those with valvular AF were on a novel anticoagulant.

Data source: A study of more than 190,000 patients participating in the PINNACLE Registry.

Disclosures: The PINNACLE Registry is funded by the ACC's National Cardiovascular Data Registry. The presenter reported having no financial conflicts.

VIEW ON THE NEWS

Dr. Jun Chiong, FCCP, comments: Direct thrombin inhibitor (DTI) use has definitely gained wide acceptance in a short period of time, mainly because of its efficacy and its stable drug level, which eliminated regular prothrombin time testing requirements that are inherent with warfarin.

Marketing including print advertisements played a significant role in its widespread use. However, it is important for prescribers to remember that it's our role to read package inserts before prescribing any drugs as well as manufacturers role to educate the medical providers about its use, contraindications, and misuse of these agents.

To date, studies on DTI for valvular atrial fibrillation failed to demonstrate benefit over warfarin.

IN THIS ISSUE

Dr. W. Michael Alberts, FCCP, is Medical Editor in Chief of *CHEST Physician*.

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Soluble ST2 protein predicts ARDS ICU mortality

BY PATRICE WENDLING
Frontline Medical News

MADRID – Elevated levels of the soluble ST2 protein were associated with higher intensive care unit mortality in patients with acute respiratory distress syndrome in a prospective pilot study.

Among 62 patients, median soluble ST2 levels were significantly higher among ICU nonsurvivors than survivors on day 1 of acute respiratory distress syndrome (ARDS) onset (4,934 pg/mL vs. 1,007 pg/mL) and at day 3 (5,720 pg/mL vs. 823 pg/mL), Dr. Marina Garcia de Acilu reported at CHEST World Congress 2014.

The soluble form of the ST2 [interleukin-1 (IL-1) receptor-like 1] protein, and its ligand, IL-33, have come under increased scrutiny in recent years for their potential role in the pathogenesis of various pulmonary diseases including ARDS.

ST2 concentrations have been reported to be elevated in patients with asthma, pulmonary fibrosis, and eosinophilic pneumonia.

ST2 concentrations have been reported to be elevated in patients with asthma, pulmonary fibrosis, and eosinophilic pneumonia, and were shown in the PRIDE (ProBNP Investigation of Dyspnea in the Emergency Department) study to predict 1-year survival among acutely dyspneic patients with pulmonary disorders admitted to the emergency department (Am. J. Clin. Pathol. 2008;130:578-84).

The current single-center, prospective study involved 62 patients admitted to the ICU with ARDS from September 2012 to September 2013. Their median APACHE II (Acute Physiology and Chronic Health Evaluation II) score was 24 (range 19-29) and their median age was 61 years. ICU mortality was 41%.

No significant differences were seen in IL-33 concentrations on day 1 or 3 between survivors and those who died, reported Dr. Garcia de Acilu of Vall d'Hebron University Hospital, Barcelona.

An ST2 level on day 1 of at least 3,672 pg/mL, however, accurately identified patients who died (area under the operator curve 0.96; *P* less than .01), and outperformed traditional APACHE and SOFA (Sequential Organ Failure Assessment) scores, with a sensitivity of 86% and specificity of 100%.

Continued on following page

VITALS

Key clinical point: ST2 is a useful early biomarker for prognosis.

Major finding: Median soluble ST2 levels were significantly higher among ICU nonsurvivors than survivors at day 1 (4,934 pg/mL vs. 1,007 pg/mL) and day 3 (5,720 pg/mL vs. 823 pg/mL).

Data source: A prospective study in 62 patients with ARDS.

Disclosures: The investigators reported no financial disclosures.

Continued from previous page

Patients with an ST2 level below this threshold on day 1 had significantly higher survival rates in a Kaplan-Meier survival analysis.

In addition, an ST2 level above 3,672 pg/mL on day 1 was the only variable in multivariate analysis associated with ICU mortality, increasing the risk of death more than 14-fold (hazard ratio, 14.7), Dr. Garcia de Acilu reported in the poster presentation.

"In ARDS patients, ST2 may be considered a useful early biomarker for prognosis, by identifying high-risk-of-death patients," the authors concluded. "Further studies, using ST2 clinically, should be performed to assess the added value in specific subpopulations or in the presence of some comorbidities."

ST2 may also prove useful as a therapeutic strategy. A recent study, also out of Barcelona, reported that human mesenchymal stem cells, genetically engineered to produce soluble ST2, further prevented IL-33 induction, but also enhanced IL-10 expression in a murine acute lung injury model. This synergy led to a substantial decrease in lung airspace inflammation and vascular leakage (Am. J. Respir. Cell Mol. Biol. 2013:49:552-62).

"This study also illustrates the potential role for targeting ST2 as a therapy for airway disorders," senior author Dr. Jordi Rello, chief of critical care at Vall d'Hebron University Hospital, said in an interview.

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VIEW ON THE NEWS

Dr. Eleanor Summerhill, FCCP, comments: A recently discovered member of the IL-1 superfamily of cytokines, IL-33 has been shown to have multiple immunomodulatory effects, but predominately induces the T–helper cell (TH-2) pathway. The soluble isoform of the IL-1 receptor (ST2) acts as a "decoy receptor" for IL-33, dampening the pro-inflammatory response. A growing body of evidence suggests that plasma levels of ST2 may serve as a useful biomarker in cardiac, rheumatologic, and pulmonary disease, including asthma, pulmonary fibrosis, eosinophilic pneumonia, and ALI/ARDS.

Dr. Garcia-Acilu and colleagues recently reported the results of a small, single-center study evaluating the prognostic value of soluble ST2 levels on day 1 in patients with ARDS, and found that the use of this biomarker outperformed both the APACHE II and SOFA scores in predicting mortality. There is also some evidence in the literature that modulation of soluble ST2 levels may be useful as a therapeutic modality.

This is a very exciting new area of investigation with significant potential impact on the future management of patients with ARDS.

Menopause isn't a culprit behind severe asthma

BY PATRICE WENDLING
Frontline Medical News

MADRID – Menopause is blamed for many things, but it's unlikely to be the reason for the increased risk of severe asthma or worse quality of life in elderly asthmatic women, a study suggests.

"The increased unadjusted asthma severity and need for health care utilization in postmenopausal women are more likely due to other factors like age and other comorbidities rather than menopause per se," Dr. Joe Zein, FCCP, said at CHEST World Congress 2014.

The investigators used a propensity score matching method to analyze the effect of menopause on asthma severity, quality of life, and health care utilization in 166 menopausal and 538 premenopausal women enrolled in the Severe Asthma Research program from 2002 to 2011.

Subsequent multivariate logistic regression analyses were used to adjust for the covariates of age at enrollment, hypertension, gastroesophageal reflux disease (GERD), and hormone therapy, which was used in only 35 menopausal women.

Compared with premenopausal women, menopausal women were older and reported less atopy and more comorbidities, such as higher body mass index, diabetes mellitus, hypertension, GERD, obstructive sleep apnea, sinusitis, and nasal polyps, said Dr. Zein, a pulmonologist at Cleveland Clinic.

Lower lung function and higher neutrophil percentage were seen in menopausal women.

DR. ZEIN

Menopausal women also had lower lung function and higher neutrophil percentage in both induced sputum and bronchoalveolar lavage fluid.

Severe asthma was present in 31% (167/538) of premenopausal and 72% (119/166) of menopausal women.

In unadjusted analysis, the risk of severe asthma was almost sixfold higher in menopausal women (odds ratio, 5.62; 95% confidence interval 3.83-8.26), but dropped dramatically in the adjusted analysis (OR, 1.46), he said.

Menopausal women also had lower average scores than did premenopausal women (4.06 vs. 4.56) on the 7-point Asthma Quality of Life Questionnaire, with 7 being "not impaired at all" and 1 being "severely impaired."

The mean difference between groups pointed to worse quality of life among menopausal women in unadjusted analysis (–0.5), but again this faded after multivariate adjustment (0.31; 95% C.I. –0.-0.93).

Similar trends were observed for health care utilization including emergency department visits (unadjusted OR, 1.33; adjusted OR, 1.15) and hospitalization (unadjusted OR, 2.93; adjusted OR, 0.70), Dr. Zein said.

Finally, an analysis stratified by menopausal status that looked at the association between enrollment age and the probability of severe asthma suggested a rise in severe asthma among premenopausal women and those in early menopause, followed by a steady decline around age 55 years. Two possible hypotheses are that insulin resistance is higher during the period around menopause and thus may worsen asthma and that estrogen levels initially rise during early menopause before declining and also may increase asthma severity, Dr. Zein said.

"We don't know exactly, but I think we should not look at menopause as one entity."

Several studies have tried to tease out the effects of menopause and aging on asthma severity, with conflicting results.

A recent study reported that menopausal women in their fifties and sixties are more than twice as likely to be hospitalized for asthma as men the same age (Ann. Allergy Asthma Immunol. 2013;111:176-81).

The Harvard Nurses Health Study, however, found that postmenopausal women who never used hormone therapy had a significantly lower age-adjusted risk of asthma than premenopausal women (Am. J. Respir. Crit. Care Med. 1995;152:1183-8).

The role of estrogen in asthma remains controversial, Dr. Zein observed. The incidence of asthma is twice as high among boys during childhood, but this switches during puberty when girls have a higher incidence of asthma as well as asthma-related hospitalizations and health care utilization, he noted.

Dr. Zein reported no financial disclosures; a coauthor reported grant monies from the National Institutes of Health.

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VIEW ON THE NEWS

Dr. Vera DePalo, FCCP, comments: Asthma severity changes over the spectrum of a lifetime with changing linkage to gender at different ages. During menopause, while there is an increased likelihood of severe asthma, there are several confounding factors, resulting in lower adjusted odds ratios, As we learn more about asthma and its associations, the complexity of its manifestations becomes more evident.

Apixiban for VTE reduced subsequent hospitalizations

BY BRUCE JANCIN
Frontline Medical News

WASHINGTON – Treating acute venous thromboembolism with the fixed-dose oral factor Xa inhibitor apixaban significantly reduces subsequent all-cause hospitalizations, compared with conventional therapy with enoxaparin followed by warfarin, according to a secondary analysis of the landmark AMPLIFY trial.

The 21% reduction in the risk of hospitalization in the apixaban group during the 6 months following the initial VTE was driven mainly by fewer hospitalizations for recurrent VTE or major bleeding. There were also significantly fewer physician office visits by patients on apixaban than for those on enoxaparin/warfarin, Dr. Margot Johnson reported at the annual meeting of the American College of Cardiology.

An analysis of the cost savings associated with this reduction in hospitalizations seen in AMPLIFY is underway and will be reported later this year, added Dr. Johnson of King's College Hospital in London.

AMPLIFY (Apixaban for the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis) was an industry-sponsored randomized double-blind study of 5,365 patients with acute symptomatic VTE who were assigned to 6 months of treatment with apixaban (Eliquis) at 10 mg b.i.d. for 7 days followed by 5 mg b.i.d. or to enoxaparin followed by warfarin. In the previously reported primary outcomes (N. Engl. J. Med. 2013;369:799-808), apixaban showed noninferiority to the conventional regimen in terms of the rate of recurrent VTE or VTE-related death, and a highly significant superiority in terms of major bleeding, with a 69% risk reduction.

BRUCE JANCIN/FRONTLINE MEDICAL NEWS

Dr. Margot Johnson reported a 21% risk reduction in admissions with apixaban vs. warfarin or enoxaparin.

Dr. Johnson reported that during the 6-month study period, 5.72% of the apixaban group had one or more hospitalizations after the initial event, compared with 7.07% of the control group. This translated to a highly significant 21% relative risk reduction. For every 74 patients treated with apixaban instead of enoxaparin/warfarin, one hospitalization was avoided. Moreover, when a hospitalization occurred in apixaban-treated patients, the mean length of stay was shorter: 10.2 vs. 11.7 days in the enoxaparin-warfarin group.

The median time to a first hospitalization was 63 days in the apixaban group, compared with 34.5 days in controls. The apixaban group's

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FDA regs would rein in e-cigarette, cigar marketing

BY ALICIA AULT
Frontline Medical News

The Food and Drug Administration's long-awaited proposal to regulate e-cigarettes, cigars, and other tobacco products as if they were cigarettes does not go far enough to protect the public, and especially children, from the harmful effects of tobacco products, including nicotine addiction, according to its critics.

And, they say, it gives manufacturers too much time to continue selling their products without oversight while the FDA takes an undetermined period of time to consider comments on the proposal and make the rule final.

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The FDA proposal extends control over e-cigarettes, cigars, and nicotine gels.

The 2009 Family Smoking Prevention and Tobacco Control Act gave the FDA authority to extend its regulation of tobacco to all tobacco-derived products. A few years ago, the agency deemed all tobacco-derived products as similar to cigarettes but had not issued any regulation until now. The new proposal would extend the FDA's power to regulate e-cigarettes, cigars, pipe tobacco, nicotine gels, water pipe (or hookah) tobacco, and dissolvable tobacco products.

"This proposed rule is the latest step in our efforts to make the next generation tobacco free," HHS Secretary Kathleen Sebelius said in a statement. The regulation would allow the FDA to determine whether products like e-cigarettes serve as a gateway to cigarette use, she told reporters.

Mitch Zeller, director of the FDA's Center for Tobacco Products, said the agency is "funding massive studies" to get a better handle on the potential benefits and risks of e-cigarettes and the patterns of use. "We have far more questions than answers about who is using e-cigarettes and how they are being used," he told reporters in a briefing.

Under the proposed rule, makers of tobacco products would have to:

► Register with the FDA and report product and ingredient listings.
► Market new tobacco products only after FDA review.
► Make direct and implied claims of reduced risk only if the FDA confirms that scientific evidence supports the claim and that marketing the product will benefit public health as a whole.
► Not distribute free samples.

FDA Commissioner Margaret Hamburg said the agency will take comments on the rule for 75 days and then, after analysis, make it final. But she would not give a timetable for when the rule would be made final.

Manufacturers who've had products on the market as of February 2007 will be required to submit applications for approval within 24 months of the final rule's effective date. During that period, they will be allowed to continue to sell their products, subject to a few regulations that will go into effect immediately. That would include a ban on retail and Internet sales to children under age 18 years; a prohibition on free samples; the requirement that companies register with the FDA; a prohibition on direct or implied claims that the products reduce the risks from tobacco use; and a prohibition on vending machine sales unless located in facility that never admits youth.

The FDA would not ban Internet sales altogether or prohibit TV ads. The agency would have to issue separate rules on marketing and promotion, said Mr. Zeller.

There's no proposed ban on flavored tobacco products. That will also require separate rules, once the agency has established jurisdiction over all the products deemed similar, said Mr. Zeller. The agency is proposing to give so-called premium cigars that meet certain criteria a pass on most of the regulation.

Dr. Margaret Foti, CEO of the American Association of Cancer Research said in a statement that FDA regulation of "all tobacco products, including e-cigarettes and cigars," is imperative and that the FDA should prohibit the sale and marketing of these products to children. "The proposed rule is an important step forward in expanding the FDA's regulation of tobacco," she added.

The Campaign for Tobacco-Free Kids lauded the FDA, but was disappointed in the decision to not regulate flavorings. The group said in a statement that the flavorings, often found in cigars or e-cigarettes, appeal to youth. It called the potential premium cigar loophole "deeply disturbing," adding: "There is no justifiable public health rationale for exempting any category of cigars.

'As long as e-cigarette companies continue to take pages from Big Tobacco's old and cynical marketing playbook, our children will remain vulnerable to the grave dangers of nicotine addiction.'

A handful of Democratic Senators and a House member who issued a recent report on the apparently concerted effort to market e-cigarettes to teenagers expressed dismay with the FDA proposal. The joint statement said: "Today, after years of waiting for the FDA to act, we are extremely disappointed by its failure to take comprehensive action to prevent e-cigarette companies from continuing to deploy marketing tactics aimed at luring children and teenagers into a candy-flavored nicotine addiction.

"As long as e-cigarette companies continue to take pages from Big Tobacco's old and cynical marketing playbook, our children will remain vulnerable to the grave dangers of nicotine addiction."

The American Cancer Society Cancer Action Network said that while the FDA's action was an important step, it was still giving manufacturers a chance to skirt oversight, especially when it came to marketing to children.

FDA Commissioner Hamburg said that the agency would move quickly. "We are eager to see this process move forward," she said.

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advantage in terms of hospitalization risk was consistent across subgroups on the basis of age, body weight, sex, and renal function.

The number of emergency department visits during the 6-month follow-up period was similar in the two study arms. However, only 5.8% of the apixaban group visited a physician's office, compared with 7.3% of controls. The reasons for these office visits were basically the same as for the hospitalizations: mostly recurrent VTEs and bleeding episodes. In the apixaban group, 35 patients had an office visit for recurrent VTE, compared with 61 controls. And 71 apixaban-treated patients made an office visit for bleeding episodes, compared with 130 controls.

Session cochair Dr. Emile R. Mohler commented on the finding that 37 patients in the apixaban group and 48 on enoxaparin/warfarin required hospitalization for recurrent VTE.

"It seems like we're not doing a good enough job there. Either both of these anticoagulants don't work well, or the patients aren't taking the medication, or we're not following up with them enough. I can't remember the last time in my own clinical practice that somebody who took their medication came back within 6 months of having a VTE. It seems strange. I think there's a lot of room for improvement," commented Dr. Mohler, professor of medicine and director of vascular medicine at the University of Pennsylvania, Philadelphia.

BRUCE JANCIN/FRONTLINE MEDICAL NEWS

Dr. Emile R. Mohler: Gaps lie in following up with patients to ensure adherence.

Dr. Johnson agreed about the room for improvement. But she added that, although the data she presented were based upon an intention-to-treat analysis, the results were the same – significantly fewer hospitalizations in the apixaban group – in a per-protocol analysis that excluded patients with less than 80% adherence to their study medication.

Session cochair Dr. John P. Cooke commented that one underutilized aspect of treatment for acute VTE is compressive support, which he said has been given short shrift in the major practice guidelines.

"Often as physicians, we give patients a pill and we think that we've treated them. Compressive support is important in VTE," stressed Dr. Cooke, chair of the department of cardiovascular sciences at the Houston Methodist Research Institute and director of the Center for Cardiovascular Regeneration at the Houston Methodist DeBakey Heart and Vascular Center.

The AMPLIFY trial was sponsored by Bristol-Myers Squibb and Pfizer. Dr. Johnson reported having no financial conflicts.

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Benzodiazepines linked to worse COPD in older adults

BY AMY KARON
Frontline Medical News

Benzodiazepine use is associated with significantly increased risks of adverse respiratory outcomes in older adults with chronic obstructive pulmonary disease, researchers reported in the European Respiratory Journal.

VITALS

Key clinical point: Use caution when prescribing benzodiazepines for COPD patients.

Major finding: New users of benzodiazepines were significantly more likely to be prescribed oral corticosteroids or respiratory antibiotics (RR, 1.45) and to visit the emergency department for COPD or pneumonia (RR, 1.92).

Data source: Retrospective population-based cohort study of 177,355 adults with COPD who were aged 66 years or older and lived in Ontario, Canada, during 2003-2010.

Disclosures: The Canadian Institutes of Health and the Institute for Clinical Evaluative Sciences funded the study. The investigators had no relevant conflict of interest.

New benzodiazepine users were 45% more likely to receive outpatient respiratory medications and were 92% more likely to visit the emergency department for respiratory reasons than were non–benzodiazepine users, reported Dr. Nicholas Vozoris of St. Michael's Hospital and the University of Toronto and his associates.

"These findings are concerning, given that benzodiazepines are known to be frequently used among older adults with COPD and in suboptimal ways," the investigators wrote.

The retrospective population-based cohort study identified 177,355 adults with COPD who were at least 66 years old and lived in Ontario, Canada, during 2003-2010. The researchers used 1:1 propensity score matching without replacement to match 48,915 new benzodiazepine users with the same number of nonusers (Eur. Respir. J. 2014 April 17 [doi: 10.1183/09031936.00008014]).

New users of benzodiazepines were significantly more likely to be prescribed oral corticosteroids or respiratory antibiotics (relative risk, 1.45) and to visit the emergency department for COPD or pneumonia (RR, 1.92).

Furthermore, in the subgroup of patients who had no exacerbation of COPD during the year before baseline, new benzodiazepine users had a significantly greater risk of receiving outpatient respiratory medications (RR, 1.63), visiting an emergency department for COPD or pneumonia (RR, 2.46), being hospitalized for either diagnosis (RR, 1.29), or dying from any cause (RR, 1.19).

The research is consistent with findings from previous smaller, shorter-duration studies, said Dr. Vozoris and his associates. They noted that their definition of COPD had a sensitivity of only 58%, which could limit the generalizability of the findings.

VIEW ON THE NEWS

Dr. Daniel Ouellette, FCCP, comments: The old paradigm of COPD as a respiratory illness has been replaced in recent years by the concept of COPD as a multisystem disorder. Neuropsychiatric conditions are commonplace among patients with COPD. Pulmonologists caring for patients with COPD frequently encounter anxiety disorders among their patients with severe respiratory disease.

Recent studies now indicate that treatment of COPD patients with benzodiazepines is associated with adverse respiratory outcomes. Clearly, respiratory physicians must use great care in prescribing such agents for their patients with COPD.

Although statistical methods were used to control for other variables in this retrospective analysis, the question remains: Are the worse respiratory outcomes in COPD patients taking benzodiazepines when compared to those not taking these agents an effect of the treatment or an effect of differences in the underlying illness?

A little PT goes a long way in hospitalized COPD patients

BY PATRICE WENDLING
Frontline Medical News

MADRID – Adding physical therapy to standard care improved self-reported quality of life in patients hospitalized with an acute exacerbation of chronic obstructive pulmonary disease in a randomized, controlled trial.

Significant gains in health-related quality of life were seen at discharge on all of the EUROQol-5D questionnaire subscales including mobility (mean 2.00 vs. 1.29), self-care (mean 1.76 vs. 1.19), usual activities (mean 2.14 vs. 1.43), pain/discomfort (mean 1.71 vs. 1.24), and anxiety/depression (mean 2.00 vs. 1.38).

Overall health, measured with the EUROQol-5D visual analog scale, also improved significantly from an average score of 57.0 to 74.4, Irene Torres-Sánchez, PT, reported at CHEST World Congress 2014.

What stands out is that the average hospital length of stay was just 8.8 days.

The physical therapy protocol included 45 minutes of daily, individualized resistance training targeting the lower limbs and controlled breathing exercises including relaxation exercises, pursed lips breathing, and active expiration, explained Ms. Torres-Sánchez, of University of Granada, Spain.

VITALS

Key clinical point: Consider prescribing physical therapy in hospitalized COPD patients.

Major finding: Overall health on the EUROQol-5D visual analog scale improved from 57.0 to 74.4 at discharge ($P = .006$).

Data source: A randomized, single-blind trial in 60 patients.

Disclosures: The investigators reported no financial disclosures.

No significant differences were found between the 30 intervention patients and 30 controls at baseline in Saint George's Respiratory Questionnaire values (63.95 vs. 63.00). Their average age was 71 years and body mass index was 27.6 kg/m^2.

Improvements were seen in the control group, but they were statistically significant, using a P value of less than .05, only for anxiety/depression (mean 1.96 vs. 1.46; P less than .001). Overall health did not improve significantly from baseline (55.42 vs. 58.96; $P = .396$), according to the poster presentation (Chest 2014;145:372A [doi:10.1378/chest.1823625]).

In two other posters reported during the same session, the investigators showed that adults hospitalized with acute COPD exacerbation walked only 255 steps per day on average (Chest 2014;145:385A [doi:10.1378/chest.1822986]).

Those who took part in the PT program, however, had improved muscle strength and steadiness and muscle endurance, although it was not uniformly significant for both legs (Chest 2014;145:369A [doi:10.1378/chest.1823630]).

The investigators reported no financial disclosures.

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VIEW ON THE NEWS

Dr. Eric Gartman, FCCP, comments: While further work would be needed in this area to confirm their data and ensure that the effects seen were not just due to the 45 minutes of daily attention the PT group received – it supports other recent studies in our field that the earlier we mobilize and encourage our patients to get out of bed, the better their functionality and outcomes. In addition to the benefit to patients, if such interventions were also shown to reduce COPD readmissions, formal implementation of these resources would become very attractive to health care teams and hospital administrators alike.

Preop sepsis drives thrombosis risk

Sepsis *from page 1*

analysis of 1,744,808 surgical procedures performed during 2005-2011 at 314 U.S. hospitals participating in the American College of Surgeons National Surgical Quality Improvement Program. This large, prospective, observational registry is known for its high-quality data.

Within 48 hours prior to surgery, 7.8% of patients – totaling more than 136,000 – had SIRS, sepsis, or septic shock. Their postoperative thrombosis rate was 4.2%, compared with a 1.2% rate in patients without sepsis. In a multivariate regression analysis adjusted for potential confounding factors, the postoperative thrombosis risk climbed with increasing severity of preoperative sepsis (see graphic).

SIRS was defined on the basis of temperature, heart rate, respiratory rate, WBC count, and/or the presence of anion gap acidosis. "Sepsis" was defined as SIRS plus infection. And septic shock required the presence of sepsis plus documented organ dysfunction, such as hypotension.

The importance of recognizing this newly spotlighted sepsis/postoperative thrombosis connection is that most of the other known risk factors for thrombosis in surgical patients, including age, cancer, renal failure, and immobilization, are nonmodifiable, Dr. Donze observed.

Among the factors known to contribute to thrombosis are a hypercoagulable state, a proinflammatory state, hypoxemia, hypotension, and endothelial dysfunction. "All of these factors can be triggered by sepsis," Dr. Donze noted.

He reported having no financial conflicts regarding this study.

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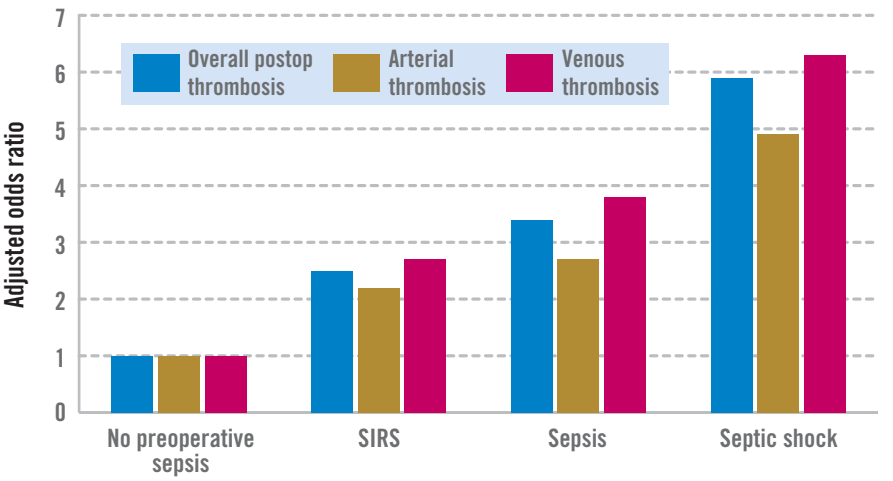
VIEW ON THE NEWS

Dr. Marcos I. Restrepo, FCCP, comments: This interesting observation links the associated risk of preoperative sepsis and any degree of sepsis severity with a higher risk of developing postoperative arterial and venous thrombosis. Therefore, it is critical to recognize and identify preoperative patients with systemic inflammatory response syndrome with a suspected or confirmed source of infection ("sepsis") in order to initiate early and appropriate thromboprophylactic measures.

Postoperative thrombosis risk, 2005-2011



Note: Based on data from 1,744,808 surgical procedures included in the American College of Surgeons National Surgical Quality Improvement Program.

Source: Dr. Donzé

FRONTLINE MEDICAL NEWS

Bed rest after ALI linked to weakness, functional impairments

BY AMY KARON
Frontline Medical News

Muscle strength returned within 12 months of ALI, but muscle weakness was associated with significant limitations in physical function and quality of life that persisted for at least another 12 months.

Duration of bed rest during acute lung injury was the most consistent predictor of muscle weakness among survivors 2 years later, according to a report in the April issue of Critical Care Medicine.

For every additional day of bed rest, survivors' muscle strength was 3%-11% lower at 24-month follow-up, said Dr. Eddy Fan of the division of critical care medicine, University of Toronto.

The results underscore the importance of evidence-based methods to reduce bed rest during critical illness, including early physical and occupational therapy, wrote Dr. Fan and his colleagues (Crit. Care Med. 2014;42:849-59).

The prospective, multisite, longitudinal study comprised 520 patients with acute lung injury, of whom 222 underwent muscle strength evaluations. During follow-up visits at 3, 6, 12, and 24 months, investigators measured extremity, hand grip, and respiratory muscle strength; anthropometric variables; and the distance patients could walk in 6 minutes. Patients completed a short-form survey on health-related quality of life.

The researchers found that patients generally recovered muscle strength within 12 months after acute lung injury, but that muscle weakness was associated with significant limitations in physical function and quality of life that persisted for at least another 12 months. Only 36% of patients received any physical therapy while in the ICU and while the average ICU stay was 13 days, patients who did receive PT went an average of 10 days before it began.

The researchers noted that they did not use nerve conduction studies, electromyography, or muscle and nerve biopsies, and did not control for factors such as outpatient rehabilitation or subsequent hospitalizations.

VITALS

Major finding: For every additional day of bed rest during acute lung injury, survivors lost up to 11% in muscle strength at 24-month follow-up.

Data source: Multisite prospective study with longitudinal follow-up conducted for 222 patients 3, 6, 12, and 24 months after acute lung injury.

Disclosures: The National Institutes of Health partially funded the research. The authors did not disclose any conflicts of interest.

VIEW ON THE NEWS

Dr. Steven Q. Simpson, FCCP, is not only an intensivist, but a former ICU patient. He said both perspectives lead him to support early occupational and physical therapy for survivors of severe acute illness.

"I can assure you that recovery from such an episode is prolonged," said Dr. Simpson. "Thanks to [my] experience, I have been especially tuned in to the recent movement among intensivists toward concern for the long-term welfare of our ICU patients, and I have been a willing participant in activities that we hope will reduce the duration of weakness and cognitive impairment that our patients experience."

At the University of Kansas Medical Center, he said, intensivists "are aggressive users of a progressive upright mobility protocol, including ambulating patients who are on the mechanical ventilator. We include physical therapy and occupational therapy orders on our admission to the ICU order set, and we use a daily checklist to ensure that the patients have been seen and are receiving active PT and OT to the full extent that they can participate."

He added that ventilated patients have daily sedation interruptions, in part so they can participate in PT and OT.

"Finally, we have a sleep management protocol in our ICU to help alleviate the exhaustion that accompanies ICU care by allowing eligible patients to sleep for at least 5 uninterrupted hours per night," he said. "Believe me, I never got that as an ICU patient!"

Ultrasound-aided fibrinolysis safe in lung embolism

BY BRUCE JANCIN
Frontline Medical News

WASHINGTON – Ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive or submassive pulmonary embolism significantly improves right ventricular function, reduces pulmonary hypertension and angiographic evidence of obstruction, and lessens the risk of fibrinolysis-associated intracranial hemorrhage, according to a prospective multicenter clinical trial.

"By minimizing the risk of intracranial bleeding, ultrasound-facilitated, catheter-directed, low-dose fibrinolysis represents a potential game changer in the treatment of high-risk pulmonary embolism patients," Dr. Gregory Piazza said in presenting results of the SEATTLE II study at the annual meeting of the American College of Cardiology.

Full-dose systemic fibrinolysis has been the go-to advanced therapy for high-risk pulmonary embolism (PE), but physicians are leery of the associated 2%-3% risk of catastrophic intracranial hemorrhage, noted Dr. Piazza, a cardiologist at Brigham and Women's Hospital and Harvard University, Boston.

SEATTLE II was a single-arm, 21-site, prospective study in which 150 patients with high-risk PE underwent treatment using the commercially available EKOS EkoSonic Endovascular System.

Twenty-one percent of patients had massive PE, defined as presentation with syncope, cardiogenic shock, resuscitated cardiac arrest, or persistent hypotension. The remaining 79% had submassive PE, with normal blood pressure but evidence of right ventricular dysfunction. All patients had to have a right ventricular/left ventricular ratio (RV/LV) of 0.9 or greater on the same chest CT scan used in diagnosing the PE. This CT documentation of right ventricular dysfunction has been associated in a meta-analysis of patients with submassive PE with a 7.4-fold increased risk of death due to PE compared to normotensive PE patients with normal right ventricular function (J. Thromb. Haemost. 2013;11:1823-32).

The primary endpoint was change in RV/LV on chest CT from baseline to 48 hours after initiation of fibrinolysis. This ratio improved from 1.55 to 1.13, for a statistically and clinically significant 27% reduction. Improvement was seen in pulmonary artery systolic pressure – a secondary efficacy endpoint – which decreased from 51.4 mm Hg before treatment to 37.5 mm Hg post procedure and 36.9 mm Hg at 48 hours. Both efficacy endpoints improved to a similar extent regardless of whether patients had massive or submassive PE.


Frontline Medical News

By minimizing the bleeding risk, this procedure could be a 'game changer,' said Dr. Gregory Piazza.

The mean Modified Miller Pulmonary Artery Angiographic Obstruction Score improved by 30%, from 22.5 pretreatment to 15.8 at 48 hours.

Three in-hospital deaths occurred. One was due to massive PE which occurred before the fibrinolysis procedure could be completed, one involved overwhelming sepsis, and one was due to progressive respiratory failure. Major bleeding occurred in 11% of patients; however, 16 of the 17 events were classified as GUSTO moderate bleeds, with only a single GUSTO severe hemorrhage. There were no intracranial hemorrhages.

The fibrinolytic agent used in SEATTLE II was tissue plasminogen activator, delivered at 1 mg/hr for a total dose of 24 mg. Patients with unilateral PE received a single device and 24 hours of infusion time. The 86% of patients who had bilateral disease got two devices and 12 hours of therapy.

The proprietary EKOS system comprises an outer infusion catheter with side holes that elute the fibrinolytic agent, and an inner core catheter with ultrasound transducers placed at regular intervals. The transducers produce low-intensity ultrasound which serves two purposes. Through a process called acoustic streaming, the low-intensity ultrasound helps push the fibrinolytic agent closer to the thrombus. Plus, the ultrasound energy causes the clot fibrin to reconfigure from a tight lattice to a more porous structure that promotes deeper penetration of the fibrinolytic, Dr. Piazza explained.

Audience members greeted the results enthusiastically. "Most of us really do believe that for safety reasons this is the way to go, rather than systemic fibrinolysis," one said.

Dr. Piazza said the next step will be to study briefer infusion times as a means of achieving faster patient improvement with reduced use of hospital resources.

The EKOS system has been approved in the United States since 2005 for blood clots in the arms and legs. Dr. Piazza received a grant from EKOS Corp., which sponsored SEATTLE II.

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Tenecteplase works, but risks may outweigh benefits

BY MARY ANN MOON
Frontline Medical News

Fibrinolytic therapy with tenecteplase prevents hemodynamic decompensation in patients with intermediate-risk pulmonary embolism but raises the risk of major hemorrhage and stroke, so its use is likely to remain controversial in this patient population, according to researchers.

Fibrinolysis is warranted for high-risk PE characterized by hemodynamic instability, but its risks may outweigh its benefits when normotensive patients have acute right ventricular dysfunction and myocardial injury but no overt hemodynamic compromise. The international PEITHO (Pulmonary Embolism Thrombolysis) trial involved 1,006 adults (median age, 70 years) at 76 sites in 13 countries; 506 were randomly assigned to a tenecteplase infusion plus unfractionated heparin, and 500 to a matching placebo infusion plus unfractionated heparin, reported Dr. Guy Meyer of Université Paris Descartes. All were followed for 30 days

The primary efficacy outcome – a composite of death from any cause or hemodynamic decompensation (including hemodynamic collapse) within 7 days – occurred in 2.6% of the tenecteplase group, significantly lower than the 5.6% in the placebo group. Hemodynamic decompensation occurred in 1.6% of the tenecteplase group vs. 5.0% of the placebo group (N. Engl. J. Med. 2014;370:1402-11).

Major bleeding occurred in 11.5% of the tenecteplase group within 7 days, compared with 2.4% of the placebo group. The fibrinolytic treatment was associated with a 2.0% risk of hemorrhagic stroke and a 6.3% rate of major extracranial hemorrhage. "Caution is warranted when considering fibrinolytic therapy for hemodynamically stable patients with PE," the researchers noted.

PEITHO was funded by Programme Hospitalier de Recherche Clinique, Federal Ministry of Education and Research, and Boehringer Ingelheim. Dr. Meyer reported ties to Boehringer Ingelheim, Leo Pharma, Bayer Healthcare, and Sanofi-Aventis.

VIEW ON THE NEWS

Dr. Frank Podbielski, FCCP, comments: The primary efficacy outcome of PEITHO was all-cause mortality *or* hemodynamic collapse. Lead investigators Dr. Konstantinides and Dr. Meyer found a significant difference in these endpoints of 2.6% in the full-dose tenecteplase group vs. 5.6% in the placebo group. Hemodynamic collapse, however, did not automatically translate into certain mortality. All-cause mortality between the groups differed by four patients, with over one-half of the patients in the tenecteplase group dying of stroke or hemorrhage. Thrombolytics remain a powerful tool for treatment of pulmonary embolism.

The potential for catastrophic complications should, however, temper enthusiasm for their use except in the direst of situations.

Shortened delirium scale predicted clinical outcomes

BY MICHELE G. SULLIVAN
Frontline Medical News

A new delirium scoring system has shown excellent correlation with clinical outcomes in hospitalized elderly patients, including length of stay, functional decline, and death, investigators report.

In both short and long form, the Confusion Assessment Methods-S (CAM-S) is designed to complement the existing CAM, Dr. Sharon Inouye and her colleagues reported in the Annals of Internal Medicine.

"The short form (5-minute completion and scoring time), which is based on the CAM diagnostic algorithm alone, is quicker and simpler to rate; however, the long form (10-minute completion and scoring time) provides a broader range of severity scores in delirium and no-delirium groups," wrote Dr. Inouye of the Institute for Aging Research, Boston, and her coauthors.

"Unlike the Delirium Rating Scale, a clinician rater is not required for the CAM-S. Instead, well-trained research assistants can reliably conduct the assessments," the researchers wrote.

Both the short-form and long-form CAM-S instruments were validated in a group of 919 patients aged 70 years or older, who were scheduled for major surgery. The cohort was drawn from two extant study groups: the ongoing SAGES (Successful Aging After Elective Surgery) study, and Project Recovery, which ran from 1995 to 1998. Delirium was first rated by the existing CAM, and then according to the two versions of CAM-S.

The short-form CAM-S rates patients on four features of the CAM: symptom fluctuation, inattention, disorganized thinking, and altered level of consciousness. The most severe score is a 7. The longer form is based on 10 features, which also include disorientation, memory impairment, perceptual disturbances, psychomotor agitation, psychomotor retardation, and sleep-wake cycle disturbance. The most severe score is a 19.

The measures had excellent correlation with each other, and with several clinical outcomes, investigators said (Ann. Intern. Med 2014;160:526-33).

Length of hospital stay increased with increasing delirium severity across both forms, with an adjusted mean stay of 6.5 days for no delirium to almost 13 days with high severity in the short form. In the long form, length of stay increased from about 6 days to 12 days.

Hospital costs also tracked severity, ranging from an adjusted mean of $5,100 for no delirium to $13,200 for severe delirium in the short form. A similar pattern emerged in the long form, ranging from $4,200 to $11,400.

Functional decline was also highly correlated with score. On the short form, it occurred in 36%-68% of patients, depending on severity. In the long form, the range was 25%-61%. Cognitive decline showed a similar pattern.

In the short form, the cumulative adjusted rates of death within 90 days ranged from 7% to 27%, depending on severity. In the long form, the range was 7%-22%.

In the composite outcome of death or nursing-home placement, results on the short form ranged from 15% to 51%, depending on severity. In the long form, the range was 13%-48%

"There may be inherent dependencies between CAM-S score and adverse outcomes," investigators wrote. "For example, patients with longer lengths of stay may have had higher CAM-S scores because of more opportunities for measurement."

The National Institute on Aging funded the study. None of the authors reported having any financial conflicts.

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VIEW ON THE NEWS

Dr. Jennifer Cox, FCCP, comments: The CAM-S delirium scoring system complements the original Confusion Assessment Method for evaluating outcomes in our elderly population. In the short or long form, they are a quick method to predict length of stay, functional decline, and death. These outcomes are of keen interest to patient's families, clinicians, and hospital administrations. Validation of the CAM-S over a broader age range of at-risk patients is needed.

Medicare panel dings low-dose CT lung cancer screens

BY REBECCA KERN
Frontline Medical News

Evidence is insufficient to support lung cancer screening with low-dose computed tomography in the Medicare population, members of the Medicare Evidence Development and Coverage Advisory Committee said at a meeting.

Specifically, the MEDCAC advisers said that, on average, they had low confidence there is adequate evidence that the benefits outweigh the harms of lung cancer screening with low-dose computed tomography (LDCT) in the Medicare population.

The Centers for Medicare & Medicaid Services accepted two formal requests to initiate a national coverage analysis on lung cancer screening with LDCT, which the U.S. Preventive Services Task Force gave a grade B recommendation for people at high risk for lung cancer based on age and smoking history.

"I think it's almost impossible to extrapolate to the Medicare population the expected results that we would get when I feel it's our obligation to first do no harm. I didn't hear that the evidence is there to support benefit beyond harm," said Dr. Curtis Mock, national medical director of UnitedHealthcare Medicare & Retirement.

Most of the MEDCAC advisers said that they were not satisfied by the Medicare-population data in the National Lung Screening Trial (NLST). That study of more than 50,000 asymptomatic adults, aged 55-74 years, showed a 16% reduction in lung cancer mortality and a 6.7% reduction in all-cause mortality when patients were screened using LDCT (N. Engl. J. Med. 2013;368:1980-91). One cancer death was averted for every 320 patients screened, and one death from all causes was prevented in every 219 patients screened.

But Medicare-eligible patients – those aged 65-74 years – represented about 25% of patients in the trial, less than the nearly 36% NLST-eligible in the U.S. population.

The MEDCAC advisers noted that they were not confident that the harms of lung cancer screening with LDCT (average effective dose of 1.5 mSv) would be minimized if implemented in the Medicare population.

"I am concerned that we don't really have a lot of data in the Medicare population, certainly not in the 75- to 80-[year-old age group], particularly on the harms in the age group that was included in NLST," said Dr. Rita Redberg, MEDCAC chair and professor of medicine at the University of California, San Francisco.

Dr. Redberg also highlighted the additional health complications with Medicare-age patients.

"Surgical mortality increases as one gets older, and the benefits of early detection tend to disappear as you get older because there are more competing causes of death," she said.

CMS will take the expert panel's recommendations into consideration as it develops its national coverage decision for lung cancer screening with LDCT, which it plans to issue by mid-November, followed by a 30-day public comment period.

Wisconsin law shields apologies from court cases

BY ALICIA GALLEGOS
Frontline Medical News

Following more than 35 other states, Wisconsin is the latest to enact a law protecting physicians from apologies being used against them in court.

Assembly Bill 120, signed by Wisconsin Gov. Scott Walker (R) in April, shields from legal evidence any statement or gesture by doctors that expresses apology, benevolence, compassion, condolence, fault, remorse, or sympathy to a patient or patient's family.

"We know that people often feel like their doctors abandon them after things go badly," said Dr. Norman Jensen, professor emeritus of internal medicine at the University of Wisconsin, Madison. "We know one of the reasons is doctors are afraid of getting sued. [The law's intent] is that doctors will feel [freer] to go and talk to their patients after an adverse action happens. We know that lawsuits are less likely if doctors would only do that."

The Wisconsin law is part of an ongoing trend among jurisdictions to safeguard physicians who apologize to patients after medical mishaps. At least 37 states have some form of apology law. Pennsylvania enacted an "I'm sorry" statute in October. While the laws center on protecting doctors who express sympathy to patients, they differ in stringency. Some shield statements of regret or condolence, but do not protect admissions of guilt or fault, Dr. Jensen said. Stronger laws, such as Wisconsin's, protect both apologetic statements and expressions of fault.

"The weak version [of the law] might be worse than none at all," said Dr. Jensen, who testified in support of the law in the state legislature. "It might mislead physicians into thinking they were protected when they really weren't."

Apology laws are not without opposition. Plaintiffs' attorneys across the country have strongly advocated against them. The Wisconsin Association for Justice (WAJ) expressed disappointment, saying the rule prevents patients from proving their medical malpractice claims and gives too much power to the medical community.

"A physician indicating regret for something that has gone wrong is one thing, but to admit to catastrophic carelessness and not be held responsible when you told the truth about what you did is another," WAJ President Christopher Stombaugh said in a statement. "The health care worker said it, people heard them say it, but now we have to go to court and pretend it didn't happen. If the purpose of the trial is to discover the truth, this law does just the opposite. It hides the truth."

The WAJ supported a less expansive version of the law that would have made statements of regret, sympathy, or benevolence by a health care provider inadmissible in court.

Apology-based initiatives have yielded significant lawsuit reductions. Communication and resolution programs involve investigating events involving inappropriate care, providing an apology to patients, and offering early compensation if necessary.

Facing a lawsuit? First steps are vital

Malpractice *from page 1*

important because a lawsuit is a marathon – not a sprint."

American Medical Association data show 60% of physicians will be sued by the time they reach 55 years of age. The average span of a medical malpractice claim from start to close is generally about 2.5 years, although many suits progress longer. While most medical liability claims do not end in trial, defense attorneys say knowing how to respond to a lawsuit can raise doctors' chances of a quicker, more ideal resolution.

First and foremost, physicians should notify their malpractice insurance carrier as soon as possible after lawsuit papers are served, said Matt Mitcham, senior vice president of claims for MagMutual Insurance Company, a medical liability insurer that operates in the Southeast. Employed physicians should immediately alert their risk management department.

"All suits have a limited time for providing a response, and there are severe consequences for not meeting these deadlines," Mr. Mitcham said. "In addition, physicians need to provide their defense team with as much time as possible to prepare a response."

Doctors should resist the desire to contact patients or their families in an attempt to work out the situation themselves, adds Mr. Fitzer, who recently shared lawsuit preparation tips in two video playlists for The Doctors Company, a national medical malpractice insurer.

"Particularly with family practice physicians, they tend to have a long and strong bond with their patients and their patients' families, and they think, 'If I just call and ask what's going on, we can just fix this all right here,' " he said. "That never works. The patient or their lawyer will take whatever you say in or out of context and use it against you."

Another action to avoid after a lawsuit filing is making additions or changes to patient records, said Mr. Mitcham. "The original records should never be altered under any circumstance," he said. "Today's forensic specialists are experts in identifying changes, and by altering records, a physician can potentially turn a defensible case into one that is indefensible."

Securing an attorney that doctors trust and with whom they can aptly communicate is also essential, said Michael F. Ball, a medical liability defense attorney and partner at McCormick Barstow, LLP, in Fresno, Calif. Most doctors may not realize they can typically choose from a panel of attorneys used by their insurer, he said. Physicians can also ask to view the attorney panel and conduct their own research before requesting a specific lawyer.

Mr. Ball counsels his clients to focus only on the task at hand during each stage of a lawsuit, rather than worry about future phases or a possible trial. For example, during the deposition stage, physicians should prepare by understanding the deposition's purpose, reading through the record, and being clear on what questions may be asked. A deposition is a witness's sworn, out-of-court testimony used to gather information as part of the discovery process.

"Some [physicians] don't review the record as closely as they should," he said. "There's no substitute for real preparation."

Additionally, depositions are a stage in which a physician's emotions may come bubbling to the surface, notes Angela Dodge, Ph.D., founding partner of Dodge Consulting & Publications, LLP, a litigation consulting firm in the Seattle-Tacoma area.

"A doctor may go into a deposition feeling very angry and resentful because a patient they believe they gave good care to is now suing," said Ms. Dodge, author of the book "When Good Doctors Get Sued: A Practical Guide for Physicians Involved in Malpractice Lawsuits, and Winning at Jury Selection." "We counsel them on the importance of setting that aside because it could

Continued on following page

VIEW ON THE NEWS

Dr. James A.L. Mathers, Jr., FCCP, comments: A 2011 study in the New England Journal of Medicine estimated that 75% of physicians in "low-risk" specialties and virtually 100% of physicians in "high-risk" specialties could expect to face a malpractice claim sometime in their career (N. Engl. J. Med. 2011;365:629-36). However, 60% of liability claims against doctors are dropped, withdrawn, or dismissed without payment, and physicians are found not negligent in over 90% of cases that do go to trial.

While there are no readily available national statistics on the actual number of claims filed, there is data, compiled by the federal government's National Practitioner Data Bank (NPDB), suggesting that the number of cases filed has been dropping in the last decade.

The NPDB issues an annual report that includes the number of medical malpractice payments made each year for the preceding 10 years. For nearly every year in the past decade, the number of medical malpractice payments made on behalf of all practitioners reported to the NPDB has decreased. Between 2002 and 2011, the number of medical malpractice payments decreased nearly 40%, declining steadily from 18,696 to 11,424.

Also, in the past 10 years, the number of medical malpractice payments reported to the NPDB, attributed to physicians and dentists, has decreased steadily from 17,155 to 10,038. Between 2003 and 2011, the total amount paid out fell from $4.5 billion to less than $3.2 billion, a 29% drop. State tort-reform laws limiting noneconomic damages, growth in risk management responses to adverse events, and the growing use of apology and disclosure likely have contributed to this trend.

Continued from previous page

interfere with" their success.

Negative emotions by doctors may be interpreted by plaintiffs' attorneys as guilt or defensiveness and used to fuel their claims, she said. Doctors should also focus only on the questions being asked during a deposition and not offer up any further or additional information. For instance, in a recent case, a doctor was asked about a specific part of his education. In response, the physician provided information about his entire medical education, including his experience operating on pigs, how pig anatomy is relevant to human medicine, and other needless details, Ms. Dodge said.

"He was so anxious to explain how he gained his expertise; he forgot that the question was [only] where and when he gained his expertise," she said.

Litigation counselors point to strong cooperation among physicians, insurers, and defense attorneys as one of the most vital components to the successful handling of a lawsuit.

"The legal system can be a very daunting place for physicians, but when the malpractice carrier and defense attorney work together as a team, they can help the physician navigate the process and hopefully win the case," Mr. Mitcham said.

Adempas (riociguat) tablets, for oral use

Initial U.S. Approval: 2013

BRIEF SUMMARY of prescribing information
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

Do not administer Adempas to a pregnant female because it may cause fetal harm *[see Contraindications (4) and Use in Specific Populations (8.1)]*.

Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception *[see use in Special Populations (8.6)]*.

For all female patients, Adempas is available only through a restricted program called the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

1.1 Chronic-Thromboembolic Pulmonary Hypertension

Adempas is indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class *[see Clinical Studies (14.1)]*.

1.2 Pulmonary Arterial Hypertension

Adempas is indicated for the treatment of adults with pulmonary arterial hypertension (PAH), (WHO Group 1), to improve exercise capacity, WHO functional class and to delay clinical worsening.

Efficacy was shown in patients on Adempas monotherapy or in combination with endothelin receptor antagonists or prostanoids. Studies establishing effectiveness included predominately patients with WHO functional class II–III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%) *[see Clinical Studies (14.2)]*.

4 CONTRAINDICATIONS

4.1 Pregnancy

Adempas may cause fetal harm when administered to a pregnant woman. Adempas is contraindicated in females who are pregnant. Adempas was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*.

4.2 Nitrates and Nitric Oxide Donors

Co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated *[see Drug Interactions (7.1), Clinical Pharmacology (12.2)]*.

4.3 Phosphodiesterase Inhibitors

Concomitant administration of Adempas with phosphodiesterase (PDE) inhibitors, including specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline) is contraindicated *[see Drug Interactions (7.1), Clinical Pharmacology (12.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

Adempas may cause fetal harm when administered during pregnancy and is contraindicated for use in women who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, advise use of acceptable contraception and obtain monthly pregnancy tests. For females, Adempas is only available through a restricted program under the Adempas REMS Program *[see Dosage and Administration (2.3), Warnings and Precautions (5.2) and Use in Specific Populations (8.1, 8.6)]*.

5.2 Adempas REMS Program

Females can only receive Adempas through the Adempas REMS Program, a restricted distribution program *[see Warnings and Precautions (5.1)]*.

Important requirements of the Adempas REMS Program include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the Adempas REMS Program prior to initiating Adempas. Male patients are not enrolled in the Adempas REMS Program.
- Female patients of reproductive potential must comply with the pregnancy testing and contraception requirements *[see Use in Specific Populations (8.6)]*.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive Adempas.

Further information, including a list of certified pharmacies, is available at www.AdempasREMS.com or 1-855-4 ADEMPAS.

5.3 Hypotension

Adempas reduces blood pressure. Consider the potential for symptomatic hypotension or ischemia in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, or concomitant treatment with antihypertensives or strong CYP and P-gp/BCRP inhibitors *[see Drug Interactions (7.2), Clinical Pharmacology (12.3)]*. Consider a dose reduction if patient develops signs or symptoms of hypotension.

5.4 Bleeding

In the placebo-controlled clinical trials program, serious bleeding occurred in 2.4% of patients taking Adempas compared to 0% of placebo patients. Serious hemoptysis occurred in 5 (1%) patients taking Adempas compared to 0 placebo patients, including one event with fatal outcome. Serious hemorrhagic events also included 2 patients with vaginal hemorrhage, 2 with catheter site hemorrhage, and 1 each with subdural hematoma, hematemesis, and intra-abdominal hemorrhage.

5.5 Pulmonary Veno-Occlusive Disease

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Therefore, administration of Adempas to such patients is not recommended. Should signs of pulmonary edema occur, the possibility of associated PVOD should be considered and, if confirmed, discontinue treatment with Adempas.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.1)]*
- Hypotension *[see Warnings and Precautions (5.3)]*
- Bleeding *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflect exposure to Adempas in two, randomized, double blind, placebo-controlled trials in patients with inoperable or recurrent/persistent CTEPH (CHEST-1) and treatment naive or pre-treated PAH patients (PATENT-1). The population (Adempas: n = 490; Placebo: n = 214) was between the age of 18 and 80 years *[See Clinical Studies (14.1, 14.2)]*.

The safety profile of Adempas in patients with inoperable or recurrent/persistent CTEPH (CHEST 1) and treatment naive or pre-treated PAH (PATENT 1) were similar. Therefore, adverse drug reactions (ADRs) identified from the 12 and 16 week placebo-controlled trials for PAH and CTEPH respectively were pooled, and those occurring more frequently on Adempas than placebo (≥3%) are displayed in Table 1 below. Most adverse events in Table 1 can be ascribed to the vasodilatory mechanism of action of Adempas.

The overall rates of discontinuation due to an adverse event in the pivotal placebo-controlled trials were 2.9% for Adempas and 5.1% for placebo (pooled data).

Table 1: Adverse Reactions Occurring More Frequently (≥3%) on Adempas than Placebo
(Pooled from CHEST 1 and PATENT 1)

Adverse Reactions	Adempas % (n=490)	Placebo % (n=214)
Headache	27	18
Dyspepsia and Gastritis	21	8
Dizziness	20	13
Nausea	14	11
Diarrhea	12	8
Hypotension	10	4
Vomiting	10	7
Anemia (including laboratory parameters)	7	2
Gastroesophageal reflux disease	5	2
Constipation	5	1

Other events that were seen more frequently in riociguat compared to placebo and potentially related to treatment were: palpitations, nasal congestion, epistaxis, dysphagia, abdominal distension and peripheral edema. With longer observation in uncontrolled long-term extension studies the safety profile was similar to that observed in the placebo controlled phase 3 trials.

7 DRUG INTERACTIONS

7.1 Pharmacodynamic Interactions with Adempas

Nitrates: Co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated because of hypotension *[see Contraindications (4.1), Clinical Pharmacology (12.2)]*.

PDE Inhibitors: Co-administration of Adempas with phosphodiesterase (PDE) inhibitors, including specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) and nonspecific PDE inhibitors (such as dipyridamole or theophylline), is contraindicated because of hypotension *[see Contraindications (4.3), Clinical Pharmacology (12.2)]*.

7.2 Pharmacokinetic Interactions with Adempas

Smoking: Plasma concentrations in smokers are reduced by 50-60% compared to nonsmokers. Based on pharmacokinetic modeling, for patients

Mergers pose legal challenges for physician-sellers

BY ALICIA GALLEGOS
Frontline Medical News

Practice mergers with physician groups and larger health systems are becoming commonplace as more doctors trade in their shingles for fewer business burdens and more stability. But as with all transactions, selling or merging a medical practice comes with legal risks.

"There are numerous complex issues, legal and otherwise, that the seller of a medical practice needs to consider, both in preparations for the sale and during the transaction," wrote health law attorney David N. Vozza in a recent article for Kern Augustine Conroy & Schoppmann, a health care litigation firm with offices in the East Coast.

One of the most significant legal considerations pertains to the correct transfer of medical records during sales and mergers, Mr. Vozza said in an interview. Under privacy requirements, all current patients must be advised that the practice is being transferred and they must have the opportunity to obtain their original records if they desire a new physician, he said. Records also must not be released to third parties without the patient's express authorization. In addition, physicians run the risk of an "abandonment" lawsuit, if patient care is compromised because of the sale or merger.

Under privacy requirements, all current patients must be advised that the practice is being transferred and they must have the opportunity to obtain their original records if they desire a new physician.

"If you know a patient has a pressing care or treatment need, that can't be delayed because you're in the middle of a sale," Mr. Vozza said. "It can't get lost in the shuffle of the transaction."

Another key consideration when merging practices is the assessment of liability cases, said Mathew J. Levy, a health law attorney and principal at Kern Augustine Conroy & Schoppmann and a coauthor of the risk management article. Physicians combining practices should be aware of any pending malpractice cases or audits of their potential partners.

"When merging with a larger group, you should be concerned with how they are doing internally," Mr. Levy said. "Are they under any audits or investigations? Have they been disciplined by the state licensure board? You have to make sure you're not accountable for" their debts or malpractice issues.

Physicians should also consider the effect their merger may have on their malpractice insurance, Mr. Levy adds. Coverage for prior actions can become challenging in the event that a physician has a claims-made policy, which offers protection only while the policy is in effect. If a claims-made policy is discontinued, the doctor must obtain "tail" cover-

Continued on following page

Continued from previous page

age to cover past actions. While the physician likely will have new coverage from the hospital or health system, many hospitals are self-insured and do not provide incoming physicians with prior act or so-called nose coverage.

Along with discussing tail coverage during a merger, doctors should also be wary of "anti-compete" clauses in contracts with larger hospitals and health systems. Such clauses prohibit physicians from working for a competitor and/or in close proximity to the hospital. Mr. Levy encourages physicians to include an exception to the non-compete clause in their contracts and discuss options in case the relationship fails.

"If not, you would be stuck and be prohibited from working in a nearby location and generating patients for your career," he said. "That's a significant issue."

Antitrust requirements should also be high on physicians' radar long before a transaction proceeds.

The Federal Trade Commission in January revised the thresholds that determine whether health care providers must notify federal antitrust authorities about pending transactions under the Hart-Scott-Rodino (HSR) Antitrust Improvements Act.

The HSR Act requires companies

Include an exception to the non-compete clause in merger contracts and discuss options in case the relationship fails. 'If not, you could be stuck and be prohibited from working in a nearby location.'

to notify government agencies if the size of the parties at issue and the value of a transaction exceed the filing thresholds. The 2014 FTC revision raised the threshold for reporting proposed mergers and acquisitions from $70.9 million to $75.9 million.

"If notification is required and you proceed to complete a transaction without filing the required notification, then you're in violation of the antitrust law," said Christine White, chair of the American Health Lawyers Association's Antitrust Practice Group and a staff attorney in the FTC's Northeast Regional Office.

Potential antitrust violations can result in government investigations, fines, legal settlements, or other discipline. Ms. White suggests that physicians review guidance on the FTC's website for more information about the HSR Act and other antitrust requirements, such as when it's acceptable to share confidential information with competitors.

"Not every sale of a physician practice will raise significant antitrust concerns. In fact, the vast majority of physician practice group consolidations do not raise major antitrust concerns. But, in certain circumstances, such as if a practice group is selling to a direct competitor or a potential competitor, the antitrust concerns may merit serious consideration," she said.

While the physician likely will have new coverage from the hospital or health system, many hospitals are self-insured and do not provide incoming physicians with prior act or so-called nose coverage.

PEG tubes ill advised at end of life

Intervention *from page 1*

with advanced dementia," said Dr. Teno of Brown University, Providence, R.I., and her coauthors. "Hospitals should educate physicians about the lack of efficacy of PEG [percutaneous endoscopic gastrostomy] feeding tubes, compared with hand feeding, in prolonging survival and preventing aspiration pneumonias and pressure ulcers in people with advanced dementia. In addition, hospitals should examine how they staff the role of attending physician and ensure coordination of care when patient hand-offs are made between different types of attending physicians."

Such education would bring all physicians up to speed with position statements against tube feeding for this group of patients. The issue sits atop the Choosing Wisely lists of both the American Academy of Hospice and Palliative Medicine and the American Geriatrics Society. The American Academy of Hospice and Palliative Medicine states that "feeding tubes do not result in improved survival, prevention of aspiration pneumonia, or improved healing of pressure ulcers. Feeding tube use in such patients has actually been associated with pressure ulcer development, use of physical and pharmacological restraints, and patient distress about the tube itself."

Dr. Eric G. Tangalos of the Alzheimer's Disease Research Center at Mayo Clinic, Rochester, Minn., agrees with the concept that tube feeding can impose even more distress on both these patients and their families. "As a medical profession and a society, we have yet to accept some of the futility of our actions and continue to ignore the burdens tube feedings place on patients, families, and the health care system once a hospitalization has come to its conclusion," he said in an interview.

Who's the attending?

Dr. Teno and her team looked at the rate of feeding tube insertion in fee-for-service Medicare patients with advanced dementia who were within 90 days of death and hospitalized with a diagnosis of urinary tract infection, sepsis, pneumonia, or dehydration. The study examined decisions made by four groups of physicians who cared for these patients: hospitalists, nonhospitalist generalists (geriatricians, general practitioners, internists, and family physicians), subspecialists, and mixed groups that included a subspecialist and either a hospitalist or nonhospitalist generalist.

The cohort comprised 53,492 patients hospitalized from 2001 to 2010. The patients' mean age was 85 years. About 60% had a do not resuscitate order, and 10% had an order against tube feeding.

The rate of hospitalists as attending physicians increased from 11% in 2001 to 28% in 2010. The portion of patients seen by a mixture of attending physicians increased from 29% in 2001 to 38% in 2010.

The rates of tube feeding were lowest when a hospitalist or nonhospitalist generalist was the attending physician (1.6% and 2.2%, respectively). Subspecialists had significantly higher rates (11%). The highest rate occurred when there were mixed groups of physicians involved in the patient's care (15.6%).

Using the nonhospitalist generalists as a reference group, the researchers found that hospitalists were 22% less likely to insert a tube overall and 35% less likely to do so when the patient had very severe cognitive and physical impairment.

Conversely, subspecialists were five times more likely to commence tube feeding for all patients and for very severely impaired patients. The mixed groups were the most likely to begin tube feeding – almost 9 times more likely overall and 9.5 times more likely for the most severely impaired patients.

"Our finding that subspecialists had a higher rate of insertions of PEG feeding tubes might reflect their lack of experience in providing care for people with advanced dementia," the authors wrote.

The fragmention factor

The mixed-physician group could be seen as a proxy for discontinuity of care among the attending physicians, they noted. Prior studies have found that such discontinuity was associated with longer hospital stays.

"There may be a lack of care coordination during patient hand offs between attending physicians that begins a cascade of events, ending with the insertion of a PEG feeding tube."

Dr. Diane E. Meier, professor of geriatrics and palliative medicine at Icahn School of Medicine at Mount Sinai, New York, and director of the Center to Advance Palliative Care, agreed that group care without a leader creates confusion.

"One of the hallmarks of modern medicine in the U.S. is fragmentation. It is typical for a person with dementia to have a different specialist for every organ system, a problem compounded in the hospital when a completely new group of specialists is brought into the care team. The problem with this abundance of doctors is that no one is really in charge of the whole patient and what makes the most sense for the patient as a person.

"Organ- and specialty-specific decision making leads to bad practices – including trying to 'solve' a feeding difficulty as if it is an isolated problem when the real issue is progressive brain failure – a terminal illness that cannot be fixed with a feeding tube."

The study questions not only the feeding tube issue, but also the wisdom of repeatedly hospitalizing elderly patients with severe dementia who could be in the last phase of life – especially for conditions that are expected complications of severe dementia. The authors suggested that there may be financial motives to admit fee-for-service patients.

"The fee-for-service system provides incentives to hospitalize nursing-home residents with severe dementia because such hospitalizations qualify the patients for skilled nursing-home services. Bundling of payments and institutional special needs plans that reverse these financial incentives may reduce health care expenditures and improve the quality of care for nursing-home residents with advanced dementia by avoiding burdensome transitions between facilities and the stress of relocation."

The National Institute on Aging funded the study. Dr. Teno made no financial declarations.

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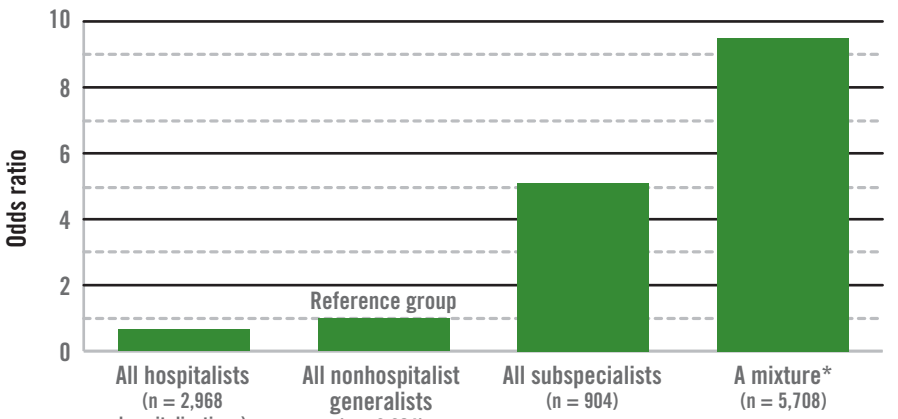
Feeding tube use in the most impaired nursing-home residents



Types of attending physicians

Usually a subspecialist and either a hospitalist or a nonhospitalist generalist

Note: Based on Medicare claims data for patients hospitalized from 2001 to 2010.

Source: Health Aff. 2014;33:675-82

PERSPECTIVE

Dr. Daniel Ouellette, FCCP, comments: The Choosing Wisely campaign sponsored by Consumer Reports and the American Board of Internal Medicine Foundation provides recommendations to help patients and providers make wise decisions about appropriate care. Both the American Academy of Hospice and Palliative Medicine and the American Geriatrics Society target the inappropriate use of feeding tubes in persons at the end of life, suggesting that such treatments do not improve patient outcomes. The news that subspecialists and primary care physicians order feeding tubes much more frequently than hospitalists is sobering information for pulmonary and critical care physicians taking care of such patients. However, future investigations focused on nutritional support and involving the patient population that pulmonologists frequently manage is likely to be complicated by the facts that such patients are or have been critically ill, and are likely to implicate a broader array of end-of-life decision making than just the provision of feeding.

PALLIATIVELY SPEAKING: In good negotiation, it's not about you

This column is based on Dr. Bekanich's recent address on "Family Meetings: The Art and the Evidence" at Hospital Medicine 2014.

BY STEPHEN J. BEKANICH, M.D., AND LEIGH A. FREDHOLM, M.D.

As a hospitalist, I stumbled and stuttered through many family meetings until I eventually found myself on more comfortable ground. Overall, I found them rewarding when they went well but stressful and deflating when they did not. The latter sensation was enough to create some avoidant behavior on my part.

After a few years of practice, my group began shadowing one another periodically on rounds to provide feedback to our colleagues in the hope of improving the quality of our communication skills. It was then that I noticed that one of my partners was a master at these meetings. A real Rembrandt. He had the ability to deliver bad or difficult news without the dynamic in the room becoming inflammatory or out of control.

I will never forget watching him mediate a disagreement between a nurse and a patient suspected of using illicit substances while hospitalized. He flipped an antagonistic, heated situation into one where the patient, nurse, and physician all agreed on putting the past to rest and forging ahead with his proposed plan. We all left the room with a *genuine* sense that we had mutual purpose. In my admiration I realized that some of these skills must be teachable.

While I didn't act on learning those communication techniques immediately after that encounter, I would eventually be formally exposed to them during my palliative medicine training. As it turns out, I still have some uncomfortable meetings with patients and families, but they come around much less frequently and when they do I now have a variety of tools to deal with challenges.

These techniques include active listening, motivational interviewing, demonstration of empathy, conflict resolution, and also negotiation. For

DR. BEKANICH

DR. FREDHOLM

the Hospital Medicine meeting audience, I dissected negotiation, citing how it and the other skills can inject vitality into your interactions.

In any negotiation, it's all about the other party. You are the smallest person in the room, the least important.

This is counterintuitive. Oftentimes at work we are trying to convince everyone how important we are. But when you enter a family meeting, the patient and his or her loved ones are the center stage. To be successful, you have to listen more and talk less. Get to understand the pictures in their heads and then summarize those thoughts and ideas back to them to show you've listened.

Make emotional payments. I don't get into the meat of the meeting until I've done that with the patient and every family member in the room. No one holds family meetings for patients who are thriving and have outstanding outcomes. We have family meetings to figure out goals in the face of terrible diseases, when elder abuse is a possibility, when insurance-funded resources are depleted, and for a host of other difficult reasons.

This means that everyone in the room is suffering, sacrificing, scared, confused, or worried. Acknowledge them. Hold them up. Thank them. Reflect on similar moments in your life and demonstrate empathy. Apologize when things haven't gone right for them at your hospital. These payments will pay handsome dividends as your relationship evolves.

***Not* manipulation.** The term negotiation might bring up images of used car salespeople. I strongly disagree. In manipulation, one side wins and the other doesn't. In negotiation, the goal is improved communication and understanding. Manipulation is about one side of the equation having knowledge that the other side is lacking and using that to achieve its means. Negotiators hope everyone at the table has the same knowledge.

This leads to two key principles of negotiations: transparency and genuineness. Patients and families are excellent at taking the temperature of the room when you sit down to meet with them. Share knowledge. Don't have any hidden agendas. Following this principle builds trust.

Be incremental. Taking patients from comfortable, familiar territory into that which is uncomfortable or unfamiliar should not be done in one giant leap. Let's use code status (CS) as an example because of the frequency with which it comes up (though I rarely talk about CS without first understanding the patient's goals and hopes).

Some patients refuse to talk about CS, so I think incrementally. I ask that they *consider* talking about CS with me in the future. Very few people refuse to consider something. Two or three days later I ask, "Have you considered talking to me about CS?" That by itself opens up the topic for conversation. In the extremely unusual case where they still won't engage, I then ask them, "What would it take for you to consider talking to me about this?" More incrementalism.

While this is not nearly an exhaustive list of negotiation techniques, we hope it is stimulating enough that you might be curious enough to learn more on your own and try incorporating this into your practice. If you're motivated to do so, please feel free to contact us for reading suggestions: E-mail sjbekanich@seton.org.

Dr. Bekanich and Dr. Fredholm are codirectors of Seton Palliative Care, part of the University of Texas Southwestern Residency Programs in Austin. Scan the code to read more columns at ehospitalistnews.com.

VIEW ON THE NEWS

Dr. Eric Gartman, FCCP, comments: We all have seen these discussions go well and been impressed by those who lead them. However, too often such conversations and family meetings are not actively pursued simply because they are "hard" – they take time and an investment of one's emotional energy. We should follow the example of many medical schools and training programs in recognizing the immense importance of gaining these skills, and foster the desire to be the one that others aim to emulate.

PRESIDENT'S REPORT: Half-year checkup

BY DR. MICHAEL H. BAUMANN, FCCP

It has been a quick 6 months since I became President of the American College of Chest Physicians (CHEST). This is a good time for a brief recap and checkup of how this new year for CHEST is going.

As in my acceptance speech in Chicago, **focus** has remained the operative word for the last 6 months. The direction we began to take in October, finishing up what we started and continuing with our core ongoing projects, has continued successfully.

New digs

We are now in our fabulous new headquarters, and I had the opportunity to attend a CHEST all-staff meeting in April at the new location. As I entered, the building was buzzing with activity. I quickly took an unscheduled detour (the staff wondered if I had gotten lost in the "new digs"). I had to see first-hand our premier course being offered in our new Innovation, Simulation, and Training Center (training center). In a word, it was great! The auditorium was divided into two ultrasound education sessions with a very engaged audience and dynamic teachers. Dr. Paul Mayo was pointing out how to discern a large pericardial effusion from a pleural effusion with great audience interaction in play. The breakout and simulation areas down the hall were full of activity as hands-on ultrasound instruction and demonstration was underway.

Education, management, innovation

Other changes to sustain our **focus** are progressing. We had our spring Board of Regents meeting in March, and many important topics and decisions were discussed and decided. Let me tell you about just a few of these:

► We will continue to **focus** on and strengthen our educational offerings (like that simulation course I just described). Part of that educational **focus** will include dissolving our Chest Regulations and Reimbursement Committee (CRR), with the education of our members about the rapidly changing healthcare environment moving under the umbrella of our education experts. As such, these activities will now report to and through the CHEST Education Committee. Our CPT and RUC efforts (that were a part of the CRR), in collaboration with the American Thoracic Society through a shared consultant, will continue as an important source of billing and coding information to educate our members.

DR. BAUMANN

► We will continue our **focus** on effectively resourcing and deploying our electronic "brain," our association management system (AMS) and accompanying technology infrastructure. The AMS and other systems will be the tools that connect all of our great work to you, our members, and to our staff. Meanwhile, the ongoing work of our registry, AQuIRE, will be shelved, as we **focus** our staff and member efforts in other vital areas, including building even better and more course offerings in our new training center, eg, expanding our health-care provider simulation and training courses.

► We continued to enhance and build, with our CHEST Enterprises team, our PREP (Professional Representative Education Program) courses. These are offered to our industry partners to train their personnel in pulmonary-, critical care-, and sleep-related medication and equipment innovations. We now do some of our PREP courses on-site at CHEST's training center.

Finally, our committee chairs and vice-chairs were at the Spring Leadership Meeting, where they had the opportunity to join the Board of Regents and attend several lectures on leadership, including how to most effectively align their committees' efforts with CHEST's strategic plan (**focus** again). Boring, you say? No, I say! If we are going to continue to offer the best in pulmonary, critical care, and sleep medicine clinical education globally, we need to continue to **focus** on our strategy. Core to that strategy is great education.

Our guest speakers at that meeting, Glen Tecker and Leon Moores, did a great job highlighting tips and tools on how to remain **focused** on our ongoing CHEST goals that help us provide the best in clinical education, so we as clinicians can provide the best possible care to our patients. These tips and tools were used by our major committees during their recent meeting at our new headquarters in April, as they aligned their great ideas with our strategic plan in preparation for next year's budget. This also provided a great chance for some of our members to see our new headquarters and to have a hand in determining our next year's **focus** areas.

CHEST

Technicians manipulate a mannequin to simulate a real-life scenario in order to educate a learner in CHEST's new Innovation, Simulation, and Training Center.

Other areas of **focus** have yielded great success, such as our CHEST World Congress 2014 in beautiful Madrid in March. In brief, we had more than 2,200 attendees from more than 78 countries and speakers from throughout the world— truly superb global clinical education for a global audience. Congratulations to Drs. Richard Irwin and Joan Soriano, our co-chairs of the meeting, and to our program committee for a great effort! You can read about this event on page 31 in this issue of *CHEST Physician*.

What else is on the horizon? Don't forget CHEST 2014 in Austin, Texas. The program is set, and the speaker invitations have gone out. We have a wonderful program lined up for you, and registration is now open at chestnet.org. Be sure to make plans to join us. Also, how are your New Year's resolutions going? Remember that list from my report in the March issue of *CHEST Physician*? If you haven't done so yet, take another look and take advantage of the great opportunities to be a part of the CHEST community. And … don't forget to make your donation to The CHEST Foundation!

This Month in *CHEST*: Editor's picks

BY DR. RICHARD S. IRWIN, MASTER FCCP

Editor in Chief

Accuracy of Point-of-Care Multiorgan Ultrasonography for the Diagnosis of Pulmonary Embolism.
By Dr. P. Nazerian et al.

The Emotional and Cognitive Impact of Unexpected Simulated Patient Death: A Randomized Controlled Trial.
By Dr. K. Fraser et al.

Short- and Medium-Term Prognosis in Patients Hospitalized for COPD Exacerbation: The CODEX Index.
By Dr. P. Almagro et al.

POINT/COUNTERPOINT
Were Industry-Sponsored Roflumilast Trials Appropriate?
Yes. *Dr. S. Suissa; and Dr. K. F. Rabe*
No. *Dr. J. Rho; Dr. N. Ho; and Dr. V. Prasad*

Pages 30a—30f

CHEST World Congress 2014 an unqualified success

BY DR. MARK J. ROSEN, MASTER FCCP
CHEST Medical Director

The idea to conduct CHEST World Congress 2014 came from among our 3,500 members who live outside the United States and Canada. The high cost of international travel precludes many members from attending the annual North American CHEST meeting, and the prospect of expanding our educational programs to a wider international audience is one of our responsibilities as a global education organization. In fact, CHEST has a decades-old history of conducting international congresses, from the first in Rome in 1950, to the last in Bali in 1996.

DR. ROSEN

CHEST's leadership and staff agreed that another international CHEST meeting was called for. After 2 years of planning, CHEST World Congress 2014 was held March 21-24, 2014, in Madrid, Spain. Organized in collaboration with the Spanish Society of Pneumology and Thoracic Surgery (SEPAR), a program was developed to offer clinical education by international faculty to delegates from around the world, using the array of proven and innovative approaches well-known to attendees at the annual CHEST meeting.

The program committee was assembled from global leaders in clinical chest medicine. The committee and congress were co-chaired by Dr. Richard S. Irwin, Master FCCP, and Editor-in-Chief of *CHEST*; and Dr. Joan B. Soriano, Director of the International Affairs Committee of SEPAR. The close cooperation of CHEST and SEPAR committee members enabled the production of the CHEST World Congress that spanned 3.5 days, Five postgraduate courses were offered on day 1 and included programs on thoracic ultrasonography, sleep medicine, thoracic imaging, the multidisciplinary approach to non-small cell lung cancer, and a review of controversies in pulmonary medicine. The next 2.5 days consisted of 142 sessions of all types and up to 21 available hours of continuing medical education, accredited by both the American and European accrediting bodies.

The program committee and congress were co-chaired by the Editor-in-Chief of *CHEST*.

DR. IRWIN

The congress either fulfilled or exceeded all expectations. More than 2,200 people from 78 countries attended. The largest contingent came from Italy, with 356 delegates, followed by the United States with 292, Spain with 236, and France with 124.

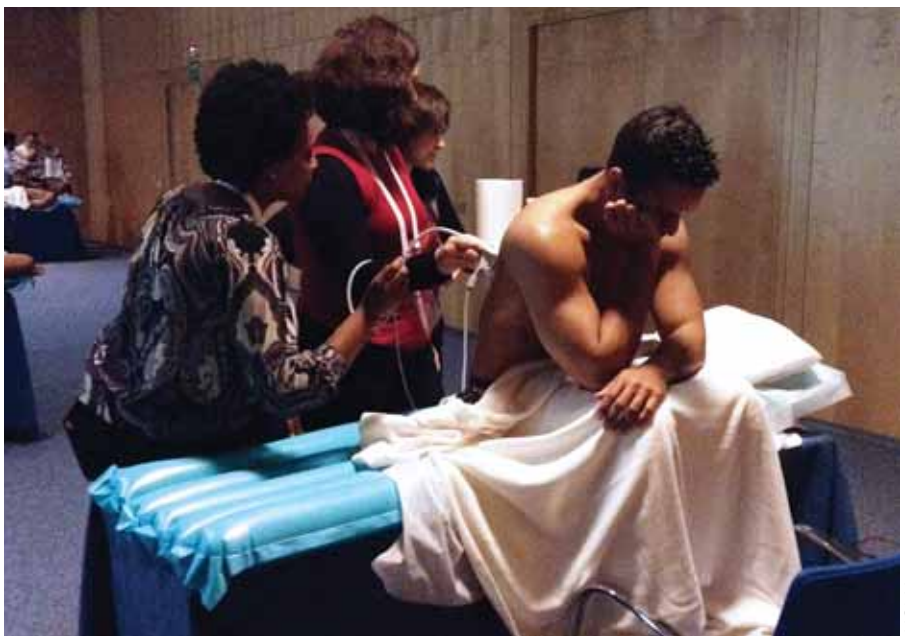
The scientific program mirrored the range of educational activities that is part of the annual CHEST meeting. Faculty from 30 countries conducted the 69 general sessions that covered the spectrum of chest medicine. The call for original research and case presentations received enthusiastic responses, with 469 abstracts and 223 case reports presented in slide and poster formats.

The prolific and honored cardiologist spoke on "The Two Pathways of Translational Research."

DR. FUSTER

The annual CHEST meeting provides a rich variety of educational experiences directed at individuals and small groups, and CHEST World Congress provided the same environment. Problem-based learning exercises and small case-based discussions have limited participation designed to promote highly interactive learning. Simulation activities are a hallmark of CHEST's educational portfolio, and CHEST World Congress offered hands-on sessions in ultrasonography, bronchoscopy, pulmonary function testing, and sleep medicine.

Two outstanding keynote speakers enriched the overall experience with their unique perspectives. Dr. Valentin Fuster, arguably the most prolific and honored cardiologist alive, spoke on "The Two Pathways of Translational Research," and on the fundamental influence of mentoring both personal growth of mentees and the growth of science. Dr. Stephen Bergman, pen name Samuel Shem and author of a classic in medical fiction, *House of God*, gave an inspiring discussion about "Staying Human in Medicine."



MCI MADRID

A hands-on course in ultrasonography was held at the meeting in Madrid. Other sessions included bronchoscopy, pulmonary function testing, and sleep medicine.

Madrid as a venue was a contributing factor to the success of the Congress. Its rich history, cultural institutions, and opportunities for great meals and entertainment surely attracted many delegates.. The atmosphere in Madrid was electrified on Sunday night with "El Clásico," the annual matchup of the Barcelona and Real Madrid teams. Some say that this is the biggest event, bigger than the World Cup, and bigger than the NFL Superbowl in the world football calendar. A few delegates got tickets, but most were fixed to televisions in hundreds of bars and restaurants around the city. Barcelona won, and the mood of Madrid cooled considerably.

CHEST World Congress 2014 owes its success to our partners in SEPAR, the international faculty who traveled long distances at their own expense, the industry partners who supported us, and the incredible dedication and hard work of the CHEST staff. We look forward to the next CHEST World Congress—please stand by for details of the dates and venue, coming soon.

Killian Centenary Award to Dr. Atul C. Mehta, FCCP

Dr. Atul C. Mehta, FCCP, of the Cleveland Clinic, was the recipient of 2014 Gustav Killian Centenary Award at the 18th World Congress for Bronchology and International Pulmonology and the 18th World Congress for Bronchoesophagology in Kyoto, Japan.

DR. MEHTA

Gustav Killian performed the first ever bronchoscopy in 1897 to remove a foreign body from the endobronchial tree. This award was created in his honor and is considered as the highest recognition in the field. It recognizes accomplished senior bronchologists whose career achievements and clinical practices have made a significant impact on the art and the science of bronchology.

Dr, Mehta is recognized worldwide for his contributions to the field of interventional pulmonology. He is one of the founders of the American Association for Bronchology and Interventional Pulmonology and the *Journal of Bronchology* and *Interventional Pulmonology*. He has been the editor in chief for that journal for over 11 years. As a Fellow of CHEST, he has led and participated in numerous committees and educational courses and currently serves as a Regent at Large on the CHEST Board of Regents.

Congratulations, Dr. Mehta!

CHEST 2014: Top training, hot music meet in Austin

When visiting Austin, what is a "can't miss"? We asked our favorite, Austin-resident CHEST members – and they overwhelmingly replied that you must hear some live music. In fact, Austin has been deemed the Live Music Capital of the World and is famous for it's annual music festival, South by Southwest. So keep an evening free or add on some extra time before or after CHEST 2014, and make sure to take in a concert at one of Austin's many music venues.

One of Austin's most famous concert venues is Austin City Limits (ACL). This theater has a 2,750-person capacity and hosts about 100 concerts a year. The theater has three levels with levels 2 and 3 featuring legendary music photography by Scott Newton and Jim Marshall. There is not a bad seat in the house; every seat is within 75 feet of the stage.

ACL is also the home for the taping of a PBS series, Austin City Limits, which is the longest running music series in American TV history. The pilot episode featured Willie Nelson in 1974. Since then, 2nd street – the road where the theater is located – was renamed Willie Nelson Blvd, and a statue of Willie Nelson stands outside the venue.

There are many other places to listen to live music in Austin. Here are a few more to check out:

► Antone's Night Club – This club is known as home of the blues in Austin. It opened in 1975 and has hosted great artists including B.B. King, Buddy Guy, Eric Clapton, and Stevie Ray Vaughn.

► The Broken Spoke – This dance hall is an authentic honky-tonk. Willie Nelson, George Straight, and Dolly Parton have performed here. This venue also includes a "memorabilia room" that is filled with photos, hats, and other country-music treasures.

► Stubb's BBQ – This famous BBQ joint hosts regional and national fan-favorites like Weezer, Los Lonely Boys, and Adele. Plus, it's known for its gospel brunch on Sundays, which includes a soulful performance, Southern-style buffet, and a make-your-own-Bloody-Mary bar.

► Threadgill's – This restaurant serves classic southern dishes and is adorned with memorabilia from it's historic past. A piano that hangs from the ceiling was played by artists as diverse as Jerry Lee Lewis to Captain Beefheart.

Austin's music scene is sure to get your toes tapping, and CHEST 2014 will move you with the latest clinical information in chest medicine. Join us October 25 - 30 for CHEST 2014, and you won't miss a beat with cutting-edge sessions and simulation training designed to update you on the latest patient-care strategies. You will be part of an international community of innovative problem-solvers. Learn more and register today at chest-meeting.chestnet.org.

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Austin is known for its vibrant nightlife and live music venues. Come for the education, and don't miss a beat.

BOOK REVIEW: A pulmonary medicine pioneer's life well lived – and passionately rendered – in biography

Editor's Note: Dr. Charles M. Hendricks, FCCP, the subject of this biography, was a Past President (1946-1947) of the American College of Chest Physicians and the first editor-in-chief of the journal Diseases of the Chest *(now called* CHEST*).*

DR. ROBERT G. JOHNSON, MASTER FCCP

It seems there was indeed a time when a man of 132 pounds could be a collegiate football player, a center in fact. It was a time when family names became anglicized. It was a time when bacterial infections could take a young healthy person's life in days or hours of his or her apparent perfect health. It was a time when getting into medical school was much easier than making a living in medicine!

This author, C.E. Campbell, is the grandson of his biographical subject. His grandfather is the unmistakable protagonist, hero, but through this perspective, a reader is treated to the origins of collegiate and professional American football, a tender brotherly love story, a glimpse of pre-Flexnerian medical education, and the origins of pulmonary medicine through the extant realities of tubercular disease.

Stretcher bearers move wounded servicemen during World War I.

The business of pulmonary medicine prior to effective antibiotics can be experienced vicariously through Dr. Charlie Hendricks' early career.

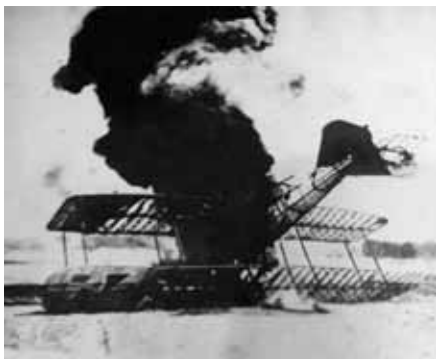
Ah! But there is much, much more. Dr. Hendricks goes to the "war to end all wars," and his service in northeast France is meticulously detailed, as we are apparently the beneficiaries of a well-kept diary or ledger. If you are a WWII aficionado, you will enjoy comparing his up-close experiences with the subsequent *guerre mondial*.

If you have wondered about the use of chemical weapons, relevant even today, Dr. Hendricks' experiences are, if not riveting, commanding of attention.

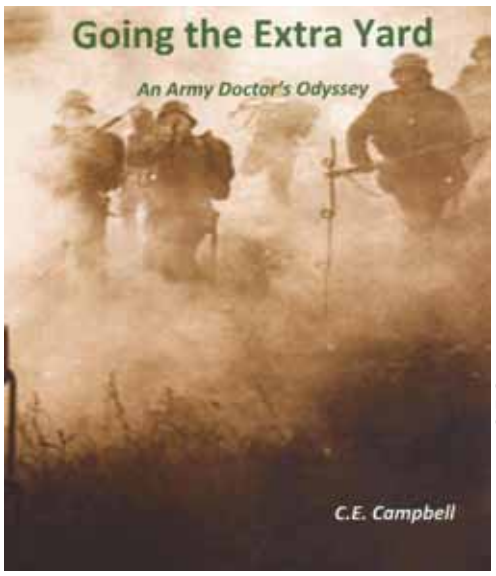
The end of the first global war seems to be a bit of a climax, but even in the dénouement, Dr. Hendricks' career holds interest as he is involved with the origin of our own professional organization, the American College of Chest Physicians, and its journal. The evolution of medicine from self-pay to a world of third-party payers lies obscured beneath the career as reported, but interested readers will be aware and interested to view this experience.

In the end, one almost sees Dr. Charlie Hendricks as having a Forrest Gump-like career. He seems to have been at the fore of such a number of exciting developments over the eras through which he lived. It is a treat for us, the readers, to experience that as well.

Dr. Charles M. Hendricks became President of the American College of Chest Physicians.



Vivid descriptions of wartime experiences permeate the book.



IMAGES COURTESY C.E CAMPBELL

Going the Extra Yard: An Army Doctor's Odyssey

By C.E. Campbell

Green Street Publications, Copyright 2013; 293 pages. Available from Amazon and from www.goingtheextrayard.com.

Reading this work forced me to reflect on what makes a great biography. Is it the story, the life, or its subject and the events therein contained? Or is it the writer, the descriptions, and the presentation that carry such a work? While well written and detailed (especially the WWI account), the distinguished author may not be a Chernow or Caro. Yet what might be lacking in objectivity and style is more, I would say much more, compensated for in passion and scrupulousness. C. E. Campbell ardently, perhaps lovingly, details his subject's life, but Dr. Charlie Hendricks lived a passionate life, and how could his biography be otherwise written?

Grant and award opportunities for 2014 – apply now

Each year, The CHEST Foundation offers grant opportunities for clinical and translational research, leadership, and volunteer community service. In 2014, grants are offered in thrombosis, lung cancer, pulmonary arterial hypertension, COPD and alpha-1 antitrypsin deficiency, women's lung health, pulmonary fibrosis, and community service. To learn more about these and the other awards, or to apply by the **May 31, 2014**, deadline, go to the Foundation's grants and awards webpage: chestnet.org/Foundation/What-We-Do/Apply-for-a-Grant.

CHEST® FOUNDATION

► The GlaxoSmithKline Distinguished Scholar in Thrombosis award is supported for $150,000 over 3 years.

► The CHEST Foundation and the Pulmonary Fibrosis Foundation Clinical Research Grant in Pulmonary Fibrosis is supported in part by InterMune, for $30,000 for 1 year.

► The CHEST Diversity Committee Young Investigator in Pulmonary, Cardiovascular, Critical Care, or Sleep Research Grant is supported in part by AstraZeneca, for $25,000 for 1 year.

DR. MCCAFFREE

► The CHEST Foundation and Respiratory Health Association Clinical Research Grant in Women's Lung Health is supported in part by AstraZeneca, for $10,000 for 1 year.

► The Clinical Research Grant in Pulmonary Arterial Hypertension is supported by Actelion, for $50,000 for 1 year.

► The CHEST Foundation and the Alpha-1 Foundation Clinical Research Grant in COPD and Alpha-1 Antitrypsin (AAT) Deficiency is supported for $25,000 for 1 year.

► The Clinical Research Grant in Lung Cancer is supported by Genentech, for $100,000 over 2 years.

► The Community Service Grants Honoring D. Robert McCaffree, MD, Master FCCP, Award range from $5,000 to $15,000 for 1 year.

NETWORKS: 24/7 coverage, tracheal replacement, FeNO testing

Pediatric Chest Medicine

24/7 in-hospital coverage: not for everybody?

When a child is critically ill, it is natural to want the most experienced provider at the bedside around the clock. As such, many institutions have instituted 24/7 in-hospital (IH) coverage by pediatric intensivists. However, the patient benefit of IH coverage remains unclear, and there are important implications related to coverage models.

Any staffing change can bring unintended consequences. The recent Survey of In-hospital Coverage by Pediatric Intensivists sought to measure coverage models' impact on faculty and house staff (Rehder et al. *Pediatrics*. 2014; 133[1]:88); Rehder et al. *Pediatric Crit Care Med*. 2014;15[2]:97).

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Despite concerns about family life and academic productivity, intensivists have favorable perceptions of 24/7 in-hospital coverage models.

While intensivists in IH models generally perceived IH coverage favorably, nights spent in the hospital was associated with burnout, and respondents expressed concern about the impact of IH coverage on their families and academic productivity. In addition, respondents questioned the preparedness of house staff for independent practice after training at institutions with IH models.

One clear outcome from these data is that all IH coverage is not created equally. Between and within institutions, there is tremendous variability in how physicians practice IH coverage. Physical presence in the hospital does not guarantee active management or increased attentiveness to patients.This variability may account for the mixed data regarding patient outcomes.

If transitioning to an IH model, institutions must evaluate the true need and design a model that will maximize patient benefit while minimizing deleterious effects on faculty and trainees. Given the workforce implications of universal IH coverage, we must proceed cautiously in making this the standard of care in all pediatric ICUs.

Dr. Kyle J. Rehder, FCCP
Steering Committee Member

Interventional Chest/Diagnostic Procedures

Advances in tracheal replacement

Tracheal replacement (TR) has been reported in the treatment of benign and malignant airway disease (Grillo. *Ann Thorac Surg*. 2002;73[6]:1995). First reported in 1979 by Rose et al (*Lancet*. 1979;1:433), TR involved the use of synthetic and cadaveric grafts. While success has been reported, results have been disappointing with long-term complication-free engraftment rarely being achieved (Grillo. *Ann Thorac Surg*. 2002;73[6]:1995; Jungebluth et al. *Thorac Surg Clin*. 2014;24[1]:97).

Recent work in TR has focused on tissue bioengineering and autologous tracheal substitution (ATS). In 2004, Macchiarini et al (*J Thorac Cardiovasc Surg*. 2004;128[4]:638) presented the first bioengineered TR utilizing a decellularized and reseed-

Continued on following page

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ed porcine jejunum scaffold. In 2008, the procedure was repeated, this time using a human donor trachea (Macchiarini et al. *Lancet*. 2008; 372[9655]:2023).

Five-year data recently reported show good graft durability, no requisite immune suppression, and the only complication being left mainstem bronchus orifice stenosis treated with stenting (Gonfiotti et al. *Lancet*. 2014;383[9913]:238). Taking another tact, Fabre et al (*Ann Thorac Surg*. 2013;96[4]:1146) report an 8-year experience of ATS in which 12 patients underwent construction of a reinforced vascularized neotrachea from a forearm free fasciocutaneous flap. Of the 12 patients treated with ATS, eight remained alive at the time of article publication without the need for immune suppression or repeated airway interventions.

Another new technology being applied to airway disease is the 3-D printer. Recent use of the 3-D printer has created bioabsorbable splints and airway models in patients with tracheobronchomalacia (Zopf et al. *N Engl J Med*. 2013; 368[21]:2043; Tam et al. *J Radiol Case Rep*. 2013;7[8]:34).

As molecular and cell biology, bioengineering, and medicine continue to collaborate, one can imagine tremendous progress in the treatment of tracheal disease. What remains is to further understand future challenges and how best to apply new technologies as they become available.

Dr. Jason Akulian
e-Community Moderator
and
Dr. David Mason, FCCP
Steering Committee Member

University of Michigan Health System

New, life-saving technology: A 3-D printer was recently used by biomedical engineers in Michigan to create a trachea and splints for a baby with tracheomalacia. The FDA granted an emergency waiver for the use.

Pulmonary Physiology, Function, and Rehabilitation

Exhaled nitric oxide

Measurement of exhaled nitric oxide (FeNO) is a simple noninvasive test useful in the diagnosis of asthma and in monitoring asthma control.

Produced by nitric oxide synthases, FeNO increases during Th2 allergic inflammation and often correlates with eosinophilic inflammation in the airways (Corren et al. *N Engl J Med*. 2011;365[12]:1088). Easily measured in the office or pulmonary function lab, elevated FeNO levels can help identify patients likely to respond to inhaled corticosteroid therapy (ICS) and to monitor adherence to ICS.

In 2011, the American Thoracic Society published guidelines recommending how FeNO should be used in clinical practice (Dweik et al. *Am J Respir Crit Care Med*. 2011;184[5]:602). The guidelines advocated the use of FeNO in the diagnosis of eosinophilic airway inflammation and in determining the likelihood of steroid responsiveness in patients with nonspecific respiratory symptoms. The ATS guidelines further suggested the use of cut points rather than reference values when interpreting FeNO levels. A level of greater than 50 parts per billion (ppb) was recommended to reflect significant ongoing eosinophilic airway inflammation, whereas eosinophilic inflammation was unlikely with a value less than 25 ppb.

The role of FeNO in the management of asthma has been controversial. Randomized controlled trials have shown conflicting results on whether FeNO-guided management results in reduced exacerbation rates. A recent study in pregnant asthmatic patients (Powell et al. *Lancet*. 2011;378[9795]:983) and a new meta-analysis by Donohue et al. (*Respir Med*. 2013;107[7]:943) demonstrated a significant reduction in asthma exacerbation rates in adult patients managed with a FeNO-based strategy. Although asthma is increasingly recognized as a complex disorder made up of different inflammatory phenotypes, these studies and others reinforce the helpful role of FeNO in detecting allergic airway inflammation and in predicting response to inhaled corticosteroids.

This month, the British National Institute for Health and Clinical Excellence (NICE) issued guidelines recommending FeNO in the diagnosis of asthma in adults and children and in guiding asthma management.

FeNO testing (CPT **95012**) is currently covered by all Medicare and Medicare Advantage plans. Currently, Medicaid payers in 36 states and many private insurance companies, including United Healthcare, WellPoint, Kaiser, and 23 of the Blue-Cross BlueShield plans, cover FeNO testing. The average reimbursement for FeNO testing is between $25 and $35.

Dr. Peter Hahn, FCCP
Steering Committee Member

Pulmonary Vascular Disease

Prostacyclin safety

Intravenous prostacyclins for pulmonary artery hypertension (PAH), such as epoprostenol and trepostinil pose particularly high risk for medication errors. Their IV delivery, potential for pump failure, short half-life (epoprostenol), and potential for death with interruption generate possibility for harm in vulnerable patients with little reserve.

A retrospective survey demonstrated that 68% of US respondents have encountered serious prostacyclin errors, including 9 deaths (Kingman et al. *J Heart Lung Transplant*. 2010;29: 841). The most common error was flushing of a dedicated central line containing prostacyclin. Our center prospectively reviewed 1216 PH patient days; 68 errors were reported - 57.4% medication-related and 13.2% related to pump malfunction (Rangarajaran et al. Culture of Safety Minimizes Serious Adverse Events in Inpatient Care of PH Patients: 1 Year Followup. Abstract. American Thoracic Society Annual International Meeting. May 2012. San Francisco).

Our focus on safety mirrors recommendations in the literature (Kingman and Chin. *Crit Care Nurse*. 2013;33[5]:32). A culture of safety is crucial, and use of consistent inpatient units is preferable. Pharmacists and nurses must maintain competencies in prostacyclin management. Detailed policies/procedures should be in place and include procedural areas, MRI, etc. Double-checks should be utilized and include the patient whenever possible. Patient dosing should be verified with specialty pharmacies upon admission, and all staff should be know how to access specialty pharmacies when needed. A dedicated line should be used for IV administration and protected from inadvertent access.

A retrospective survey demonstrated that 68% of US respondents have encountered serious prostacyclin errors, including 9 deaths.

With the future advancement of PHA PH care centers, focus on patient safety should continue to increase with specific policy requirements for participating programs. Multicenter research is needed to further characterize prostacyclin practices and establish best practices for safe delivery.

Dr. Timothy Williamson, FCCP
Steering Committee Member

SLEEP STRATEGIES: Implantable stimulator: A PAP alternative

FDA approves hypoglossal nerve device, paving new way to relief for select OSA patients.

BY DR. LAUREN TOBIAS AND DR. CHRISTINE WON

Ask anyone who treats patients with sleep apnea what they consider the biggest challenge in their management and most will

DR. TOBIAS

DR. WON

agree: convincing patients to regularly use positive airway pressure (PAP) therapy. Despite our best efforts to improve PAP tolerability, a significant proportion of patients remains unable to use it. Estimates of adherence rates range from 30% to 70% across studies.

The February 2014 issue of *CHEST Physician* highlighted a recent study exploring a novel treatment alternative for certain patients with sleep apnea. Investigators in the Stimulation Therapy for Apnea Reduction (STAR) trial enrolled a select group of sleep apnea patients with difficulty accepting or adhering to PAP therapy and surgically implanted a hypoglossal nerve stimulator designed to open the upper airway (Strollo et al. *N. Engl. J. Med.* 2014;370[2]:139).

The study was sponsored by the manufacturer, which recently secured U.S. Federal Drug Administration (FDA) approval for the device and is expected to make it commercially available later this year.

The principle behind this therapy is straightforward. It is known that sleep apnea patients lose tone in many of the upper airway muscles that normally maintain a patent airway. The genioglossus muscle is the largest upper airway dilator muscle, and its contraction results in protrusion of the tongue and stiffening of the anterior pharyngeal wall. Augmenting stimulation of this muscle may, therefore, increase airway patency, making it a reasonable therapeutic target for obstructive sleep apnea (OSA).

How the device works

The stimulator sits in a pocket under the skin in the right mid-infraclavicular area. It connects to two tunneled leads: a sensing lead extending to the intercostal muscles to detect ventilation efforts and a stimulating lead extending superiorly to the hypoglossal nerve under the tongue. Stimulation of the nerve moves the tongue forward slightly, opening the upper airway. Patients are able to turn the device on before sleep and off upon awakening with a handheld remote control.

Stimulation of the hypoglossal nerve moves the tongue forward slightly, opening the upper airway. Patients can turn the device on and off with a handheld remote control.

Their results

The trial's results were impressive. Among a total of 126 patients enrolled, the median apnea-hypopnea index (AHI) at 12 months decreased by 68%, from 29 to 9 events per hour. The oxygen desaturation index (ODI) also decreased significantly, from 25 to 7 events per hour. Using the definition of success often employed in the surgical literature, namely a reduction in AHI by at least 50% to a residual level less than 20 per hour, they found that two-thirds of patients were "responders" to the therapy. In order to prove that the device was responsible for this improvement rather than changes in the patients' disease over time, a randomly selected group of responders had their devices turned off for 1 week, allowing these subjects to serve as their own longitudinal controls. Indeed, patients' disease worsened significantly with the devices deactivated,

Continued on page 42

Obstructive sleep apnea complicates atrial fibrillation

BY MITCHEL L. ZOLER
Frontline Medical News

WASHINGTON – About 18% of U.S. patients with atrial fibrillation also have a diagnosis of obstructive sleep apnea, and the confluence of the two appeared linked to increased hospitalizations and further progression of atrial fibrillation, based on a registry of more than 10,000 U.S. atrial fibrillation patients.

Patients who have OSA and atrial fibrillation and who are treated with CPAP show a 34% relative drop in the rate of AF progression.

Patients who have AF and OSA and who are treated with continuous positive airway pressure (CPAP) show a reduced rate of AF progression, Dr. Jonathan P. Piccini Sr. said at the annual meeting of the American College of Cardiology.

"We know that if obstructive sleep apnea is treated [with CPAP], the AF burden can be dramatically reduced," Dr. Piccini, an electrophysiologist at Duke University in Durham, N.C.

Analysis of 1,624 OSA patients showed that 937 (58%) used CPAP during follow-up as a treatment for OSA. Comparison of the CPAP users and nonusers showed no significant difference in outcomes during follow-up for all-cause death, hospitalizations, cardiovascular events, or major bleeding events, but there was a statistically significant, 34% relative drop in the rate of AF progression among CPAP users compared with nonusers.

The data Dr. Piccini and his associates analyzed came from the Outcomes Registry for Better Informed Treatment (ORBIT)-AF, which starting in 2010 enrolled more than 10,000 AF patients from 172 U.S. locations with a variety of practice settings and followed them for more than 2 years. Their medical records showed that at enrollment, 1,841 of the 10,132 enrolled AF patients (18%) had also been diagnosed with OSA. Patients with OSA averaged 69 years old, while those without the disorder averaged 76 years old. Those with OSA had an average body mass index of 34 kg/m^2, compared with 28 kg/m^2 among those without OSA. Patients with OSA also had higher prevalence rates of dyspnea and fatigue than the enrolled AF patients without OSA.

MITCHEL L. ZOLER/FRONTINE MEDICAL NEWS

"We know that if obstructive sleep apnea is treated [with CPAP], the AF burden can be dramatically reduced," Dr. Jonathan P. Piccini Sr. reported.

During 2 years of follow-up, the two subgroups had similar rates of all-cause death, cardiovascular events, major bleeding events, and AF progression, but after multivariate adjustment, patients with OSA had a 12% higher rate of hospitalizations than did patients without OSA, a statistically significant difference.

The ORBIT-AF registry is sponsored by Johnson & Johnson. Dr. Piccini has received remuneration from Johnson & Johnson, Forest Laboratories, and other companies.

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Pulmonologist

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Continued from page 40

with AHIs rising to pre-implantation levels. The device use also appeared to result in modest improvements in both sleepiness and sleep-related quality of life.

Although adverse effects were reported as minor, they occurred fairly often. Forty percent of participants reported discomfort when the device was active, and 21% reported tongue soreness, likely exacerbated by movement of the tongue across the teeth during periods of stimulation. Eighteen percent of subjects reported tongue weakness after surgery, resolving over a period of days to weeks. Two patients experienced discomfort severe enough to necessitate repositioning and fixation of the device, and one elected to have the device removed.

Study participants were significantly leaner than typical patients with OSA. It seems reasonable to assume that more obese patients would have less of a response to nerve stimulation.

A closer look

The major limitations of this study stem from its participant selection. Patients were overwhelmingly male (83%), averaging 55 years of age. They were significantly leaner than typical patients with OSA, with a mean BMI of 28.4 kg/m^2. It seems reasonable to assume that more obese patients would have less of a response to nerve stimulation, since excessive laryngeal soft tissue is less likely to be the main contributor to their obstruction; moving the tongue forward should not significantly affect their pathophysiology. The authors admit as much, stating that their exclusion of patients with a BMI over 32 was based on feasibility studies showing that such patients were less favorable candidates for the procedure.

Furthermore, of the nearly 1,000 patients initially recruited for this study, about half were excluded for having AHIs outside the study's defined range (AHI 20-50). An additional 5% each were excluded for having concurrent central apnea (at least 25% of episodes), positional OSA (nonsupine AHI less than 10), or complete concentric collapse of their palate during sleep endoscopy. Based on the exclusion of the majority of screened subjects, we should be cautious in generalizing the results of the trial to our own clinical practices. Careful patient selection will be key to ensuring comparable success in real-world patients.

Finally, the manuscript contained no discussion of adherence to the device. While patients undoubtedly activated the stimulators while monitored during the sleep studies they underwent during the trial, we do not know how often they actually turned them on when unmonitored at home. Only time and experience will tell whether the frequently reported adverse events interfere with adherence. Ultimately, the question is whether this therapy reduces not just AHI but the adverse cardiovascular and cognitive sequelae of untreated OSA. While this procedure seems akin to pacemaker implantation, a common intervention with which we have all become familiar, it is not clear that the risks of infection and the frequency of battery replacement will be similar. Larger and longer-term studies are needed to better elucidate these outcomes and determine if other side effects develop over time, potentially related to longitudinal effects of repetitive stimulation of the hypoglossal nerve with every breath, every night, for years.

Comparative cost analyses have yet to be done, but it is difficult to imagine how upper airway stimulation could possibly compete with PAP in regard to this metric. Costs will derive not just from the device but also the multiple extra physician visits to assess its appropriateness. There is the cost of the implantation itself, a sleep endoscopy to assess for concentric palatal collapse (which makes patients less favorable candidates), the pre-op surgical consultation, and follow-up surgical visits. Patients will also require an additional sleep study after implantation to see whether the device is effectively eliminating sleep-disordered breathing. One can only speculate about the benefits that might be achieved by devoting equivalent money and time to improving PAP adherence.

While this procedure seems akin to pacemaker implantation, it is not clear that the risks of infection and the frequency of battery replacement will be similar.

Putting these results into perspective

Even with the strikingly positive results from STAR, it is important to note that only two-thirds of patients saw AHI reductions by at least 50%. In contrast, PAP is able to reduce apneas to the normal range (AHI less than 5) in the majority of patients. With PAP still the safest, most effective, and best-studied therapy available, efforts may be better directed at promoting its regular use. What strategies does the evidence support? Ensuring that patients' initial experiences with PAP are optimized may be key: one study found that adherence 3 days into therapy was predictive of PAP use at 1 month (Budhiraja et al. *Sleep 2007;*30[3]:320). Humidification of the airway and intensive cognitive-behavioral therapy interventions have also shown benefit (Weaver and Grunstein *Proc Am Thorac Soc.* 2008; 5[2]:173). While there is no convincing evidence that one particular mask is superior to another, our experience suggests that trying a variety of interfaces helps patients find one that facilitates better adherence.

Treatment options for OSA remain limited. Many current choices, including nasal expiratory positive airway pressure devices, oral appliances, and uvulopalatopharyngoplasty (UPPP), are less effective than CPAP. Few patients are willing to undergo more invasive surgeries such as maxillomandibular advancement and tracheostomy, despite their superior efficacy. With risks seemingly similar to those of UPPP while being effective for more severely affected patients than are typically referred for that surgery, the hypoglossal nerve stimulator occupies a unique niche among these therapies. For a highly selected, nonobese population with severe OSA or high cardiovascular risk who are unable to tolerate PAP therapy, the hypoglossal nerve stimulator may represent a leap forward in PAP alternatives with promising early data to support its use.

Dr. Tobias is a fellow in the section of Pulmonary, Critical Care, and Sleep Medicine; and Dr. Won is an Assistant Professor of Medicine in the section of Pulmonary, Critical Care, and Sleep Medicine and Medical Director of the Yale Sleep Center, Yale University School of Medicine, New Haven, Connecticut.

EDITOR'S COMMENT

This month, Dr. Tobias and Dr. Won discuss the potential role of hypoglossal nerve stimulation in the management of sleep apnea. Data on the efficacy of this treatment option have been long awaited by patients and providers alike, given the issues with positive airway pressure adherence and the lesser efficacy of currently available PAP alternatives. Unfortunately, while the therapy seems to show promise in a select subgroup of patients with obstructive sleep apnea, current data suggest a number of physiologic and anatomic characteristics that serve as relative contraindications, limiting the generalizability of study results to many patients.

While providers managing patients with sleep-disordered breathing should familiarize themselves with the risks and benefits of this new treatment option, it will be critical to carefully select appropriate patients to refer for electrical stimulation of the hypoglossal nerve; failure to do so would lead to a shock to the caregiver, as well as to the patient's tongue.

Dr. David Schulman, FCCP
Section Editor

Cortisol level, not ODI, predicted neurocognitive effects

BY AMY KARON
Frontline Medical News

Nocturnal cortisol levels explained up to 16% of changes in learning, memory, and working memory in patients with obstructive sleep apnea, a study showed. But severity of OSA did not itself predict neurocognitive impairment, said Dr.

VITALS

Key clinical point: Nighttime cortisol level is an indicator of cognitive impairment.

Major finding: Nighttime cortisol levels accounted for 9%-16% of variance in learning, memory, and working memory.

Data source: A cohort study of 55 men and women with obstructive sleep apnea.

Disclosures: The work was funded by University of California, San Diego, grants. The authors had no conflicts.

Kate M. Edwards of the University of Sydney in Lidscombe, Australia, and her associates, who conducted the study at the University of California, San Diego.

"These findings suggest that OSA-related alterations in [hypothalamic-pituitary-adrenal] activity may play a key role in the pathophysiology of neuropsychologic impairments in OSA," the investigators wrote (Sleep Med. 2014;15:27-32).

The researchers enrolled 55 men and women with OSA and measured blood cortisol levels every 2 hours for 24 hours. Participants underwent polysomnography the next night and took a battery of tests to assess seven cognitive domains. The oxygen desaturation index (ODI) was used as an index of OSA severity.

In univariate analyses, the mean apnea-hypopnea index, ODI, and nighttime cortisol levels were significantly associated with global deficit scores and particularly with domains of learning, memory, and working memory, said the investigators. In hierarchical linear regression analyses, nighttime cortisol levels accounted for 9%-16% of variance in the three domains, while ODI (apnea) severity did not predict additional variance, they reported.

"Our data are in line with the literature reporting that chronic exposure to elevated physiologic cortisol levels is associated with a decline in neurocognitive function and hippocampal structure," the investigators said. "The functional effects of cortisol on reduced memory function have been demonstrated by experimental cortisol treatment and stress-induced cortisol level increases."

The treatment of OSA with CPAP [continuous positive airway pressure] has been reported to show improvements in some aspects of neuropsychologic function, though findings are inconsistent," the investigators wrote.

"It may yield interesting data if future studies address the possibility that CPAP treatment effects on neurocognitive function are mediated by alterations in [hypothalamic-pituitary-adrenal] function, specifically reductions in nighttime cortisol levels."