### **EXAMPLES ST**<sup>®</sup> Physician THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS



"I suspect that genetics may play a big role in the results," said Dr. Aparna Swaminathan of Duke University.

### **Poor lung function as** child tied to ACOS

BY KATIE WAGNER LENNON Frontline Medical News

hildren with poor lung function will be more likely to develop asthmachronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS), suggesting that prevention of this disease should be attempted in early life, a study shows.

While other research has found that patients with poor lung function in early life have poor lung function as adults, this was the first study to investigate the relationship between childhood lung function and ACOS in adult life, according to Dinh S. Bui of the University of Melbourne, and his colleagues.

The study, published in the American Journal of Respiratory and Critical Care Medicine, used multinomial regression models to investigate associations between childhood lung parameters at age 7 years and asthma, COPD, and ACOS at age 45 years (Am J Respir Crit Care Med. 2017 Feb 1. doi: 10.1164/rccm.201606-1272OC).

"We found that ACOS participants showed evidence of persistently lower FEV, [forced expiratory volume] in 1 second] and FEV<sub>1</sub>/FVC [forced vital capacity] from childhood. This suggests that poorer childhood lung function tracked to early adult life, leading to impaired max-See ACOS · page 4

### Norepinephrine shortage linked to septic shock deaths

Hospitals had more deaths when deficient

BY AMY KARON Frontline Medical News

national shortage of norepinephrine in the United States was associated with higher rates of mortality among patients hospitalized with septic shock, investigators reported.

Rates of in-hospital mortality in 2011 were 40% during quarters when hospitals were facing shortages and 36% when they were not, Emily Vail, MD, and her associates said at the International Symposium on Intensive Care and Emergency Medicine. The report was published simultaneously in JAMA. The link between nor-

epinephrine shortage and death from septic shock persisted even after the researchers accounted for numerous clinical and demographic factors (adjusted odds ratio, 1.2: 95% confidence interval, 1.01-1.30; P = .03), wrote Dr. Vail of Columbia University, New York (JAMA. 2017 Mar 21. doi: 10.1001/ jama.2017.2841).

Drug shortages are common in the United States, but few studies have explored their effects on patient outcomes. Investigators compared mortality See Septic shock • page 7

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### Pulmonary embolism common in patients with AE-COPD

#### BY JIM KLING Frontline Medical News

FROM CHEST

bout 16% of patients Awith unexplained chronic obstructive pulmonary disease acute exacerbations (AE-COPD) had an accompanying pulmonary embolism (PE), usually in regions

that could be targeted with anticoagulants, according to a new systematic review and meta-analysis.

About 70% of the time an AE is a response to infection, but about 30% of the time, an AE has no clear cause, the authors said in a report on their research (CHEST. 2017

March;151[3]:544-54). There is a known biological link between inflammation and coagulation, which suggests that patients experiencing AE-COPD may be at increased risk of PE.

The researchers reviewed and analyzed seven studies, comprising 880 patients. See AE-COPD · page 8







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### Low FEV<sub>1</sub> nearly triples ACOS risk

ACOS from page 1

imally attained lung function," the researchers said.

"The study highlights that low childhood lung function is a risk factor for COPD (and ACOS) independent of smoking," they noted. The 1,355 study participants who had postbronchodilator (post-BD) lung function available were categorized into the following four mutually exclusive groups at age 45 years based on their asthma and COPD status: having neither asthma nor COPD (unaffected) (n = 959); having asthma alone (n = 269); having COPD alone (n = 59); having ACOS (n = 68).

Once adjusted for the sampling weights, the prevalence of current asthma alone was 13.5%, COPD alone was 4.1%, and ACOS was 2.9%. The researchers defined COPD at age 45 years as post-BD FEV<sub>1</sub>/FVC less than the Global Lung Initiative lower limit of normal. Because the associations between childhood lung function and both ACOS and COPD alone were nonlinear, the patients were grouped into quartiles based on their character-

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istics, such as their percent predicted FEV<sub>1</sub> and percent predicted FEV<sub>1</sub>/FVC at 7 years, the investigators said.

Patients in the lowest quartile for FEV<sub>1</sub> percent predicted at 7 years were 2.93 times more likely to have ACOS, compared with patients in the other quartiles for FEV<sub>1</sub> percent predicted. Patients in the lowest quartile

for FEV<sub>1</sub>/FVC percent predicted at 7 years were 16.3 times more likely to have ACOS and 5.76 times more likely to have COPD alone, compared with patients in the higher quartiles.

The researchers found large variation in childhood lung function among patients in the lowest quartiles for FEV<sub>1</sub> and FEV<sub>1</sub>/FVC. To account for this, they conducted a sensitivity analysis, which excluded those with less than 80% predicted  $FEV_1$  and  $FEV_1/FVC$  (n = 76 and 13, respectively). The associations between lung function measures and diseases in adulthood for patients in the lowest quartiles differed slightly following this adjustment. The sensitivity analy-

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sis showed that patients in the lowest quartile for  $\text{FEV}_1$  had an odds ratio of 2.4 for ACOS and that those patients in the lowest quartile for  $\text{FEV}_1/\text{FVC}$  had an odds ratio of 5.2 for COPD alone and 15.1 for ACOS.

A sensitivity analysis that excluded patients with remitted asthma from the unaffected group showed childhood FEV<sub>1</sub> was more strongly associated with ACOS for patients in the lowest quartile, compared with patients in the highest quartile (OR, 7.0; 95% confidence interval, 2.7-18.3). This same analysis found that patients from the lowest quartile and second quartile for childhood FEV, /FVC were 6.8 and 3.9 times more likely to have COPD, respectively, compared with patients in the other quartiles. This sensitivity analysis also found that patients in the first quartile for FEV<sub>1</sub>/FVC were 19.1 times more likely to have ACOS, and patients in the second quartile for FEV, /FVC were 5.3 times more likely to have ACOS.

The researchers analyzed data from the Tasmanian Longitudinal Health Study, which began in 1968 when Tasmanian children born in 1961 and attending school in Tasmania were studied with respiratory health surveys and prebronchodilator (pre-BD) spirometry measurements. The most recent survey started in 2002. Survey respondents who had participated in past follow-up studies and/or reported symptoms of asthma or cough were invited to participate in a more detailed laboratory study from 2006 to 2008. That study included completing a questionnaire, pre-BD and post-BD spirometry, and skin prick testing. The predicted and percent predicted values for spirometry were derived from the Global Lung Initiative reference equations

The final multinomial model was adjusted for childhood asthma, maternal smoking, paternal smoking during childhood, and other factors.

History of active smoking was significantly more frequent in patients with ACOS (73.5%) and COPD alone (73%) than in the unaffected (57%) groups. Childhood asthma, maternal asthma, and atopy were more prevalent in the ACOS and asthma alone groups. ACOS and COPD participants had a higher prevalence of maternal smoking during childhood.

Individuals with ACOS had the lowest pre-BD FEV<sub>1</sub> (percent predicted values) over time. Those with COPD alone or ACOS had significantly lower pre-BD FEV<sub>1</sub>/FVC (percent predicted values) at all time points, when patients were assessed, compared with unaffected participants. "Participants with COPD alone had significantly higher *Continued on following page* 

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#### Continued from previous page

FVC at 7 and 13 years, while ACOS participants had significantly lower FVC at 45 years," the researchers said.

"There was no evidence of effect modification by childhood lung infections, childhood asthma, maternal asthma, maternal smoking, or paternal smoking during childhood on the associations between childhood lung function and the disease groups," they noted.

The study was limited by its "relatively small sample sizes for the ACOS and COPD alone groups" and the absence of post-BD spirometry at 7 years, they added.

The researchers concluded that "screening of lung function in school-aged children may provide an opportunity to detect children likely to have ongoing poorer lung health, such as those with lung function below the lower limit of normal,"

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and that "[multifaceted] intervention strategies could then be implemented to reduce the burden of COPD and ACOS in adulthood.'

Asked to comment on the study, Aparna Swaminathan, MD, a pulmonary/critical care fellow at Duke University, Durham, N.C., and a Duke Clinical Research Institute fellow, said she would want to know "what is driving the effects in the study" before designing an intervention.

"I suspect that genetics may play a big role in the results, and there is increasing interest in learning how genetics are involved in COPD. A better understanding of the risk factors for lower lung function in children may also provide targets of intervention. The groups with ACOS and COPD have higher rates of maternal smoking, and while this study determined that the association between childhood low lung function and development of COPD and ACOS is independent of

I N THIS ISSUE

Vera A. De Palo, MD, MBA, FCCP, is Medical Editor in Chief of CHEST Physician.

maternal smoking, maternal smoking still seems like a good area to target," she said in an interview.

It would also be interesting to further study the first quartile of patients, she added. "The clinical



A population of children with low lung function today may be experiencing relatively less asthma.

**DR. GARTMAN** 

disease for this quartile of patients covers a wide range of severities. I would be interested in dividing this group up further and learning the outcomes of their lung function and development of COPD and ACOS."

Aggressively treating childhood asthma and poor lung function is one method that may have altered the destiny of the children with lower lung function, if it had been used, said Eric Gartman, MD, FCCP, in an interview.

Using inhaled corticosteroids and other medications for maintenance control, reducing and monitoring impairment, educating patients and patients' guardians on triggers, avoiding triggers, and having an action plan for changing therapy based on symptoms or measured flows are ways to aggressively treat such conditions, said Dr. Gartman, assistant professor of medicine at Brown University, Providence, R.I. He cited avoiding exposure to smoke, environmental pollutants, and living near highways, for those with low childhood function, as interventions that might prevent people with low lung function from later developing COPD.

Dr. Gartman added that differences between the availability of medication for children with asthma today and at the time of the study may mean there are differences between the children with low lung function in the study and those children who have low function today. A population of children with low lung function now may be experiencing relatively less asthma and more chronic lung disorders brought on by prematurity or cystic fibrosis, he noted. "As such, identification of poor function in today's young children may carry with it a significantly different set of interventions and challenges," Dr. Gartman said.

While asthma in children is better controlled now than it was at the time of the study, because the researchers did not provide any information about the asthma control of the study participants, "it [is] hard for me to say if better asthma drugs in those children would have made a difference in longterm outcomes of COPD and ACOS as an adult," Dr. Swaminathan noted.

The best thing we currently can do for children with low lung function is try and determine the underlying cause and treat any active diseases [such as asthma] that we can. This study reminds us of the need to keep searching for causes of low lung function that may be reversible," she said.

The investigators recommended future research to understand the Continued on following page

MEDICAL COMMUNICATIONS



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### **STEMI team repurposed for rapid treatment of PEs**

BY TED BOSWORTH Frontline Medical News

WASHINGTON – The in-hospital team responsible for rapid management of ST-elevation myocardial infarction (STEMI) may also be the right team to manage pulmonary embolism (PE), according to a pilot study associating this approach with rapid treatment times and low overall mortality rates.

Even though treatment

approaches were not

PE on an urgent basis

for delivery of care and

standardized, the protocol

for diagnosing and managing

produced encouraging times

outcomes, Dr. Kendall noted.

The data from the pilot study suggest that arming the STEMI team with a protocol for managing PE "is an effective means to care for patients with massive and submassive pulmonary embolism," said Michael R. Kendall, MD, of the University of Southern California, Los Angeles. He presented the findings at the 2017 Cardiovascular Research Technologies meeting.

There are obvious parallels between STEMI and PE. Like

STEMI, PE requires rapid diagnosis, triage, and when appropriate, an endovascular procedure. This led the USC investigators to consider a formal pilot study to test the premise that the STEMI team is in a position to deliver urgent care and good outcomes to PE patients.

The objective of the pilot study was "to evaluate treatment times and clinical outcome for patients with massive and submassive PE using a dedicated PE protocol," Dr. Kendall explained. Massive PE was defined as hemodynamic instability with systolic blood pressure below 90 mm Hg or requiring inotropic support. Submassive PE was defined as systolic BP greater than 90 mm Hg with right heart dysfunction, such as a dilated right ventricle and elevated troponin levels. Over an 18-month period beginning in June 2014, 40 PE patients were treated. The average age was 55 years, 50% were obese, 32% had renal insufficiency, 30% had recent surgery or had recently been immobilized, 30% had a history of deep venous thrombosis, and 28% had an active malignancy. At 43%, the largest single source of cases was the emergency department (ED), while 38% were transferred in from other centers, and 19% were al-

ready hospitalized at the time of the PE.

All patients underwent computed tomographic pulmonary angiography (CTPA) as part of the diagnostic procedure prior to an invasive angiogram. Patients received one or more different treatments upon confirmation of the PE, including catheter-directed thrombolytics, rheolytic thrombectomy, mechanical fragmentation, mechanical aspiration, and surgical pulmo-

nary embolectomy. Inferior vena cava filters were used as appropriate.

At presentation, 10% were in cardiac arrest, 22% required intubation, and 12% required extracorporeal membrane oxygenation. On the basis of the diagnostic studies, 57% had a massive PE, and the remainder had submassive disease.

The average time from door to CTPA among those presenting to the ED was roughly 5 hours. It took, on average, an additional 2 hours from CTPA to an invasive angiogram, and another 3 hours to treatment, producing a total average door to treatment time of 10 hours.

Most patients received rheolytic thrombectomy, often with another form of treatment, such as catheter-directed thrombolytics, but 15% were treated with anticoagulation alone. Although a few patients improved sufficiently to obviate the need for an invasive procedure, the remainder of the patients received anticoagulation alone because of contraindications for invasive strategies or treatment refusal.

The average length of a hospital stay was 15 days. Bleeding events occurred in 10% of patients and 18% required a blood transfusion. Survival to hospital discharge was 82%. Although there was no control group, this rate of survival was considered favorable in the context of the severity of the PE.

Overall, delivery of urgent care for PE by a STEMI team was found feasible. Even though treatment approaches were not standardized, the protocol for diagnosing and managing PE on an urgent basis produced encouraging times for delivery of care and outcomes, according to the data presented by Dr. Kendall. Because of the differences in the composition and function of the STEMI team, Dr. Kendall indicated that it is difficult to predict similar success at other centers, but the findings overall were considered positive.

The senior author of the study, David M. Shavelle, MD, also at USC, suggested that the program there might be a template. He believes that the STEMI team has the skills to deliver prompt PE care, and he believes that this approach would be appropriate at other centers. He also suggested that such formal programs may be useful in establishing better treatment protocols.

"For PE, there are no clear guidelines for treatment time intervals, such as time from door to endovascular treatment," Dr. Shavelle observed. He said that the wide variation of devices currently being used for treatment complicates efforts to develop clear clinical protocols and measure outcomes, and he "would like to see more standardization of treatment and registries to address these areas."

Dr. Kendall reported no financial relationships.

### Continued from previous page

risk factors for lower lung function in children. They called for studies that address "the risk factors over adulthood that interact with lower lung function to increase the risk of rapid lung function decline."

The study was supported by a National Health and Medical Research Council of Australia research grant; the University of Melbourne; Clifford Craig Medical Research Trust of Tasmania; the Victorian, Queensland, & Tasmanian Asthma Foundations; The Royal Hobart Hospital; Helen MacPherson Smith Trust; GlaxoSmithKline; and John L Hopper. Five authors were supported by the research grant; the others reported no conflicts. Dr. Swaminathan and Dr. Gartman had no disclosures.

### At nadir, 56% got top vasopressor

Septic shock from page 1

rates among affected patients during 3-month intervals when hospitals were and were not using at least 20% less norepinephrine than baseline. The researchers used Premier Healthcare Database, which includes both standard claims and detailed, dated logs of all services billed to patients or insurance, with minimal missing data.

A total of 77% patients admitted with septic shock received norepinephrine before the shortage. During the lowest point of the shortage, 56% of patients received it, the researchers reported. Clinicians most often used phenylephrine instead, prescribing it to up to 54% of patients during the worst time of the shortage. The absolute increase in mortality during the quarters of shortage was 3.7% (95% CI, 1.5%-6.0%). Several factors might explain the link between norepinephrine shortage and mortality, said the investigators. The vasopressors chosen to replace norepinephrine might result directly in worse outcomes, but a decrease in norepinephrine use also might be a proxy for relevant variables such as delayed use of vasopressors, lack of knowledge of how to optimally dose vasopressors besides norepinephrine, or the absence of a pharmacist dedicated to helping optimize the use of limited supplies.

The study did not uncover a dose-response association between greater decreases in norepinephrine use and increased mortality, the researchers noted. "This may be due to a threshold effect of vasopressor shortage on mortality, or lack of power due to relatively few hospital quarters at the extreme levels of vasopressor shortage," they wrote.

Because the deaths captured included only those that occurred in-hospital, "the results may have underestimated mortality, particularly for hospitals that tend to transfer patients early to other skilled care facilities," the researchers noted.

The cohort of patients was limited to those who received vasopressors for 2 or more days and excluded patients who died on the first day of vasopressor treatment, the researchers said.

The Herbert and Florence Irving Scholars Program at Columbia University provided funding.

One coinvestigator disclosed grant funding from the National Institutes of Health and personal fees from UpToDate. The other investigators reported having no conflicts of interest.

### **CF** patients live longer in Canada than in U.S.

BY MARY ANN MOON Frontline Medical News

People with cystic fibrosis (CF) survive an average of 10 years longer if they live in Canada than if they live in the United States, according to a report published online March 14 in Annals of Internal Medicine.

Differences between the two nations' health care systems, including access to insurance, "may, in part, explain the Canadian survival advantage," said Anne L. Stephenson, MD, PhD, of St. Michael's Hospital, Toronto, and her associates.

Previous studies have suggested a significant survival gap between Americans and Canadians with CF, but their conclusions were "problematic" because of inherent differences between the two countries in registry data, which complicated direct comparisons. Dr. Stephenson and her associates used several statistical strategies to adjust for these differences, and confirmed the discrepancy in survival by analyzing information for 45,448 U.S. patients and 5,941 Canadian patients treated at 110 U.S. and 42 Canadian specialty centers from 1990 through 2013.

Overall there were 9,654 U.S. deaths and 1,288 Canadian deaths during the study period, for

### **VIEW ON THE NEWS**

**Susan Millard, MD, FCCP, comments:** This study highlights that more investigations need to be done comparing the two systems. Is the



life expectancy related to insurance issues, compliance with follow-up visits, colonization with resistant organisms, or frequency of transplantation, for example? These questions need to be answered quickly to help advocate for the health of cystic fibrosis patients!

nearly identical overall mortality between the two countries (21.2% and 21.7%, respectively). However, the median survival was 10 years longer in Canada (50.9 years) than in the United States (40.6 years), a gap that persisted across numerous analyses that adjusted for patient characteristics and clinical factors, including CF severity.

One particular difference between the two study populations was found to be key: Canada has single-payer universal health insurance, while the United States does not. When U.S. patients were categorized according to their insurance status, Canadians had a 44% lower risk of death than did U.S. patients receiving continuous Medicaid or Medicare (95% confidence interval, 0.45-0.71; *P* less than .001), a 36% lower risk than for U.S. patients receiving intermittent Medicaid or Medicare (95% CI, 0.51-0.80; *P* = .002), and a 77% lower risk of death than U.S. patients with no or unknown health insurance (95% CI, 0.14-0.37; *P* less than .001), the investigators said (Ann. Intern. Med. 2017 Mar 14. doi: 10.7326/M16-0858).

In contrast, there was no survival advantage for Canadian patients when compared with U.S. patients who had private health insurance. This "[raises] the question of whether a disparity exists in access to therapeutic approaches or health care delivery," the researchers noted.

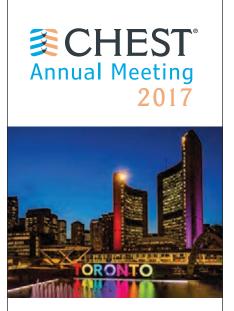
This study was supported by the U.S. Cystic Fibrosis Foundation, Cystic Fibrosis Canada, the National Institutes of Health, and the U.S. Food and Drug Administration. Dr. Stephenson reported grants from the Cystic Fibrosis Foundation and fees from Cystic Fibrosis Canada. Several of the study's other authors reported receiving fees from various sources and one of those authors reported serving on the boards of pharmaceutical companies.

### **Five studies identified PE location**

**AE-COPD** from page 1

Among the authors' reasons for conducting this research was to update the pooled prevalence of PE in AE-COPD from a previous systematic review published in CHEST in 2009.

The meta-analysis revealed that 16.1% of patients with AE-COPD were also diagnosed with PE (95%





confidence interval, 8.3%-25.8%). There was a wide range of variation between individual studies (prevalence, 3.3%-29.1%). In six studies that reported on deep vein thrombosis, the pooled prevalence of DVT was 10.5% (95% CI, 4.3%-19.0%).

Five of the studies identified the PE location. An analysis of those studies showed that 35.0% were in the main pulmonary artery, and 31.7% were in the lobar and inter-lobar arteries. Such findings suggest that "the majority of these embolisms have important clinical consequences," the authors wrote.

The researchers also looked at clinical markers that accompanied AE-COPD and found a potential signal with respect to pleuritic chest pain. One study found a strong association between pleuritic chest pain and AE-COPD patients with PE (81.0% versus 40.0% in those without PE). A second study showed a similar association (24.0% in PE versus 11.5% in non-PE patients), and a third study found no significant difference.

The presence of PE was also linked to hypotension, syncope, and acute right failure on ultrasonography, suggesting that PE may be associated with heart failure.

### VIEW ON THE NEWS

**Vera A. De Palo, MD, MBA, FCCP, comments:** Many of us have been trained with the clinical pearl, "If you think PE, treat PE." This work helps to illuminate another clinical scenario, the acute exacerbation



of COPD, where PE may play a role in the clinical course and outcome. The authors advise to think of PE in those acute exacerbation COPD patients with pleuritic chest pain and signs of heart failure. Clinical suspicion should play a role in determining the diagnostic testing. This knowledge may not only help us to recognize more cases where pulmonary embolism may play a role, but may help us provide treatment earlier and may reduce mortality from this serious clinical disease.

Patients with PE were less likely to have symptoms consistent with a respiratory tract infection. They also

Thirty-five percent of the PEs were in the main pulmonary artery, and 31.7% were in the lobar and inter-lobar arteries, suggesting that "the majority of these embolisms have important clinical consequences," the authors noted.

tended to have higher mortality rates and longer hospitalization rates compared with those without PE.

The meta-analysis had some limitations, including the heterogeneity of findings in the included studies, as well as the potential for publication bias, since reports showing unusually low or high rates may be more likely to be published, the researchers noted. There was also a high proportion of male subjects in the included studies.

Overall, the researchers concluded that PE is more likely in patients with pleuritic chest pain and signs of heart failure, and less likely in patients with signs of a respiratory infection. That information "might add to the clinical decision-making in patients with an AE-COPD, because it would be undesirable to perform [computed tomography pulmonary angiography] in every patient with an AE-COPD," the researchers wrote.

The study received no funding. The authors reported having no financial disclosures.

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### **Corticosteroids reduce risks in elective extubation**

**BY BIANCA NOGRADY** *Frontline Medical News* 

FROM CHEST

Prophylactic corticosteroids before elective extubation could significantly reduce postextubation stridor and the incidence of reintubation, particularly in patients at high risk of airway obstruction, suggests a systematic review and meta-analysis.

While current guidelines for the management of tracheal extubation call for prophylactic use of corticosteroids in patients with airway compromise, Akira Kuriyama, MD, of Kurashiki Central Hospital in Japan, and coauthors noted that there is an outstanding question as to which patients are most likely to benefit.

Writing in the Feb. 20 online edition of CHEST, they reported on an analysis of 11 randomized, controlled trials of prophylactic corticosteroids given before elective extubation, involving 2,472 participants (CHEST. 2017 Feb 20. doi: 10.1016/j. chest.2017.02.017).

They found that the use of prophylactic corticosteroids was associated with a significant 57% reduction in the incidence of postextubation airway obstruction, laryngeal edema, or stridor, and a 58% reduction in reintubation rates, compared with placebo or no treatment.

A subgroup analysis showed that

the benefit in reduction of postextubation airway events was evident only in the six trials that selected patients at high risk of airway obstruction, identified by a cuff-leak test (relative risk, 0.34), and was not seen in trials with an unselected patient population. Similarly, the reduced incidence of reintubation was evident in trials of high-risk individuals (RR, 0.35) but not in the general patient population.

The authors noted that, while the latest systematic reviews had shown that corticosteroids reduce the incidence of postextubation stridor and reintubation, only one review examined the efficacy in high-risk populations and even then, it was a pooled subgroup analysis of only three trials.

"The numbers needed to prevent one episode of postextubation airway events and reintubation in individuals at high risk for postextubation airway obstruction were 5 (95% confidence interval, 4-7) and 16 (95% CI, 8-166) respectively," they wrote, noting that routine administration of corticosteroids before elective extubation is not recommended.

"While the use of prophylactic corticosteroids was associated with few adverse events, it is reasonable to use the cuff-leak test as a screening method, and administer prophylactic steroids only to those who are at risk

### VIEW ON THE NEWS

**Daniel Ouellette, MD, FCCP, comments:** A recent CHEST evidence-based guideline on liberation from mechanical ventilation suggested the administration of corticosteroids to high-risk patients failing a cuffleak test in order to prevent re-intubation and avoid postextubation airway complications. Now, a systematic review by Kuriyama et al. published in CHEST has found evidence that high-risk patients failing a cuff-leak test have improved postextubation outcomes when given corticosteroids upon elective extubation.



Both reviews are limited by a lack of consistency among the individual studies in terms of the protocol for performing the cuff-leak. Consensus for the optimal cuff-leak algorithm must be developed so that physicians can identify the at-risk populations.

of developing postextubation obstruction, given our study findings."

Two of the six trials that identified high-risk individuals used a cuff-leak volume less than 24% of tidal volume during inflation, three used a cuff-leak volume of less than 110 mL, and one used a cuff-leak volume less than 25% of tidal volume.

"This potentially indicates that cuff-leak testing, while applied with varying cut-off values, might be able to select those at similar risk for airway obstruction and underlines the importance of screening for high-risk patients," the authors said.

The researchers also noted that the longer patients were intubated, the lower the effect size of prophylactic corticosteroids on both postexutubation airway events and reintubation.

"Patients thus tended to benefit from prophylactic corticosteroids to prevent postextubation airway events and subsequent reintubation when the duration of mechanical ventilation was short," they wrote.

The authors noted that the included trials did differ in terms of populations, corticosteroid protocols, and observation periods.

However, they pointed out that the statistical heterogeneity in their primary outcome analysis was due to the risk of postextubation airway obstruction.

The authors declared no conflicts of interest.

### Incompatible Type A plasma safe for resuscitation protocol

BY MICHELE G. SULLIVAN Frontline Medical News

HOLLYWOOD, FLA. – Incompatible Type A plasma appears to be a safe and effective part of an initial resuscitation protocol for trauma patients who need a massive transfusion.

There were no increases in morbidity, mortality, or transfusion-related acute lung injury among 120 patients who received Type A plasma, compared with those who got compatible plasma, Bryan C. Morse, MD, said at the annual scientific assembly of the Eastern Association for the Surgery of Trauma.

Type AB blood products are preferred for initial transfusions for trauma patients with unknown blood type. While type AB blood products are universally acceptable to patients, they are also in short supply. In an attempt to mitigate this shortage, some trauma centers are relying on anecdotal data, much drawn from real-life combat experience dating from World War II to present times, suggesting that Type A plasma is safe for initial resuscitation protocols. But the body of data from well-constructed trials is small, said Dr. Morse of Emory University, Atlanta. Thus, EAST sponsored this retrospective registry study, which examined outcomes in 1,536 trauma patients who received plasma transfusions as part of a massive transfusion protocol from 2012 to 2016.

The primary endpoints were overall morbidity, and mortality at four time points: 6 and 24 hours, and 7 and 28 days. Eight trauma centers contributed data to the study.

The group was largely male (75%) with a mean age of 37 years. Patients were seriously injured, with a mean Injury Severity Score (ISS) of 25. About 60% suffered from blunt-force trauma. Among the entire group, 120 (8%) received incompatible type A plasma.

About 28% of patients (434) experienced an adverse event. These were numerically but not significantly more common among the incompatible A plasma group (35% vs. 28%; P = .14). Events included acute respiratory distress syndrome (6% vs. 7.6%), thromboembolism (9% vs. 7%), pneumonia (19% vs. 15%), and acute kidney injury (8% each).

There were two cases of transfusion-related acute lung injury, both of which occurred in the compatible type A group.

Mortality was similar at every time point: 6 hours (16% vs. 15%), 24 hours (25% vs. 22%), 7 days (35% vs. 32%), and 28 days (38% vs. 35%).

A multivariate regression model controlled for treatment center, ISS, units of packed red cells given by 4 hours, mechanism of injury, Type A plasma incompatibility, and age.

In the morbidity analysis, only ISS and units of red blood cells at 4 hours were associated with a significant increase in risk (odds ratio, 1.02). Incompatible Type A plasma did not significantly increase the risk of morbidity.

In the mortality analysis, units of red cells, ISS, and age were significantly associated with increased risk. Again, incompatible Type A plasma did not significantly increase the risk of death.

Dr. Morse had no financial declaration.

### LMWH cut venous thromboembolism risk

BY MICHELE G. SULLIVAN Frontline Medical News

HOLLYWOOD, FLA. – Low-molecular-weight heparin (LMWH) decreased the risk of venous thromboembolism in trauma patients significantly more than did unfractionated heparin, a large state database review has found.

It also was associated with a 37% decrease in overall mortality, compared with unfractionated heparin, Benjamin Jacobs, MD, said at the annual scientific assembly of the Eastern Association for the Surgery of Trauma.

"Given these data, we feel that LMWH should be the preferred prophylactic agent in patients with trauma," said Dr. Jacobs of the University of Michigan, Ann Arbor. He extracted data describing thromboembolism prophylaxis among 37,868 trauma patients included in the Michigan Trauma Quality Improvement Program from 2012 to 2014. The patients were treated at 23 hospitals around the state. They received either unfractionated or LMWH as their only clot-preventing protocol. LMWH was given at either 40 mg every day or 30 mg twice a day. The comparator was unfractionated heparin at 5,000 U either two or three times a day. The preferred method was LMWH, which 83% of patients received, compared with 17% who got the unfractionated heparin. Most patients who got LMWH received the 40 mg/day dose (70%). Most who got unfractionated heparin received 5,000 U three times a day (87%).

Both types of heparin reduced the risk of all thromboembolic outcomes, and both doses of LMWH significantly reduced the risks. However, the 40mg/day dose was significantly more effective than the twice-daily 30-mg dose in reducing the risk of venous thromboembolism (VTE) and deep vein thrombosis (DVT). Risk reductions for pulmonary thrombosis (PT) and mortality were not significantly different between the doses.

Compared with unfractionated heparin, LMWH decreased the risk of VTE by 33%; of PT by 48%; and of DVT by 27%. It also reduced the risk of death by 37%, compared with the unfractionated type.

When Dr. Jacobs grouped the patients according to Injury Severity Score (ISS), he saw a consistently higher benefit among patients with lower scores. For example, LMWH significantly reduced the risk of PT by 59% in patients with an ISS of 5-14. In those with an ISS of 25 or higher, the drug was associated with a 20% increased risk, although that wasn't statistically significant. There was a similar finding in DVT. LMWH reduced the risk by 18% in those with an ISS of 5-15, and by 50% among those with an score of 16-24 – both significant reductions. Among those with an ISS of at least 25, the risk was 18% higher; although, again, it was not a significant finding. Curiously, the mortality benefit was stronger among sicker patients. The benefit was nonsignificant among those with an ISS of less than 25 but for those above 25, the mortality risk reduction was a significant 45%.

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### **SCHEST** Physician THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

### Intensive ventilation precedes lesser complications

**BY AMY KARON** Frontline Medical News

ddition of 10 cm H<sub>2</sub>O to positive end-expiratory volume (PEEP) during mechanical ventilation was followed by significantly lessened pulmonary complications in hospitalized patients who developed hypoxemia after cardiac surgery, participating in a single-center, randomized trial.

This "intensive" alveolar recruitment strategy yielded a median pulmonary complications score of 1.7 (interquartile range, 1.0-2.0), compared with 2.0 (IQR, 1.5-3.0) among patients who underwent ventilation with a PEEP of 20 cm  $H_2O$ , Alcino Costa Leme, RRT, PhD, said at the International Symposium on Intensive Care and Emergency Medicine. The report was published simultaneously online March 21 in JAMA.

Intensive alveolar recruitment nearly doubled the odds of a lower pulmonary complications score (common odds ratio, 1.9; 95% confi-

### VIEW ON THE NEWS

### **High PEEP for all?**

igh PEEP "not only recruits collapsed lung tissue, but can also lead to lung overdistension. If lung collapse is extensive, as in patients with ARDS [acute respiratory distress syndrome], and maybe also in patients with postoperative ARDS, the balance between benefit (i.e., recruitment of lung tissue), and harm (i.e., lung overdistension), tips toward benefit. If there is very little lung collapse, as in critically ill patients without ARDS or patients during surgery, this balance could go in the other direction."

The clinical trial by Leme and his colleagues "provides another brick in the evidence wall of lung protection. However, it remains unclear which patients benefit most from ventilation with a high [positive end-expiratory pressure] level."

Ary Serpa Neto, MD, MSc, PhD, and Marcus J. Schultz, MD, PhD, are at the Academic Medical Center, Amsterdam. They reported having no conflicts of interest. These comments are from their editorial (JAMA. 2017 Mar 21. doi: 10.1001/ jama.2017.2570). dence interval, 1.2-2.8; P = .003), Dr. Leme and his associates reported. The study comprised 320 adults who developed hypoxemia imme-

diately after undergoing elective cardiac surgery at the Heart Institute (Incor) of the University of São Paulo. The median age of the patients was 62 years, and none had a history of lung disease. Pulmonary complications were scored between 0 (no signs or symptoms) and 5 (death), the investigators noted (JAMA. 2017 Mar 21. doi: 10.1001/jama.2017.2297).

The intensive alveolar recruitment strategy consisted of three 60-second cycles of lung inflation with a positive end-expiratory pressure of 30 cm

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### CRITICAL CARE MEDICINE 19

 $\rm H_2O$ , pressure-controlled ventilation, driving pressure of 15 cm  $\rm H_2O$ , respiratory rate of 15/min, inspiratory time of 1.5 seconds, and  $\rm FIO_2$  of 0.40. Between and after inflations, patients received assist-controlled or pressure-controlled ventilation, with driving pressures set to achieve a tidal volume of 6 mL/kg of predicted body weight, an inspiratory time of 1 second, PEEP of 13 cm  $H_2O$ , and minimum respiratory rate to maintain  $PaCO_2$  between 35 and 45 mm Hg.

The "moderate strategy" consisted of three 30-second inflations under continuous positive airway pressure mode at 20 cm H<sub>2</sub>O and  $\rm FIO_2$  of 0.60. Between and after inflations, patients received assist or control volume-controlled ventilation (decelerating-flow waveform), tidal volume of 6 mL/kg of predicted body weight, inspiratory time of 1 second, PEEP of 8 cm H<sub>2</sub>O, and FIO<sub>2</sub> of 0.60, at a minimum respiratory rate that main-

tained PaCO<sub>2</sub> at 35-45 mm Hg. "[The] use of an intensive alveolar recruitment strategy compared with a moderate recruitment strategy resulted in less severe pulmonary complications during the hospital stay," the investigators wrote. On average, intensively managed patients *Continued on following page* 

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had shorter stays in the hospital (10.9 vs. 12.4 days; P = .04) and in the intensive care unit (3.8 vs. 4.8 days; P = .01) than did moderately managed patients. Intensive management also was associated with lower rates of hospital mortality and barotrauma,

but the differences in these less common outcomes did not reach statistical significance.

"To our knowledge, this is the first study to show a significant effect of lung recruitment maneuvers on clinical outcomes, which objectively resulted in modest reductions in ICU and hospital length of stay," the researchers wrote. "This is especially noteworthy considering that the control group was also receiving protective lung ventilation with low [tidal volume] and moderate PEEP levels. Thus, the major difference between treatment groups was the intensity of lung recruitment."

FAPESP (Fundação de Amparo e

Pesquisa do Estado de São Paulo) and FINEP (Financiadora de Estudos e Projetos) provided partial funding. Dr. Leme had no disclosures. Senior author Marcelo Britto Passos Amato, MD, PhD, disclosed research funding from Covidien/ Medtronics, Dixtal Biomedica, and Timpel SA.

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### **Dexmedetomidine improves sedation in sepsis**

**BY AMY KARON** Frontline Medical News

se of dexmedetomidine improved sedation among ventilated patients with sepsis, but did not significantly cut mortality rates or increase ventilator-free days in a multicenter, open-label randomized controlled trial.

Twenty-eight days after the start of mechanical ventilation, cumulative

mortality rates were 23% among patients who received dexmedetomidine and 31% among those who did not (hazard ratio, 0.7; 95% confidence interval, 0.4-1.2; P = .2), Yu Kawazoe, MD, PhD, and his associates reported at the International Symposium on Intensive Care and Emergency Medicine. The report was simultaneously published in JAMA.

"The study may have identified a Continued on following page

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clinically important benefit of dexmedetomidine – an 8% reduction in 28-day mortality – that did not demonstrate statistical significance ... " wrote Dr. Kawazoe of Tohoku University Graduate School of Medicine, Sendai, Japan. "Physicians may consider an 8% difference in 28-day mortality to be clinically significant, but this study was underpowered to detect this difference."

Dexmedetomidine often is used for sedation during ventilation, but its effects on mortality and ventilator weaning are poorly understood, the researchers noted. However, this highly selective alpha<sub>2</sub>-adrenergic agonist has been found to suppress inflammation and to protect organs, and "can improve patients' ability to communicate pain compared with midazolam and propofol," the researchers wrote. Therefore, they randomly assigned 201 patients with sepsis at eight intensive care units in Japan to receive sedation with or without dexmedeto-

midine. Both arms received fentanyl, propofol, and midazolam, dosed to achieve Richmond Agitation-Sedation Scale (RASS) scores of 0 (calm) during the day and –2 (lightly sedated) at night (JAMA. 2017 March 21. doi: 10.1001/jama.2017.2088).

The dexmedetomidine group spent Continued on following page

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### CRITICAL CARE MEDICINE 23

### A quarter of cultures were carbapenem-resistant

**BY LUCAS FRANKI** Frontline Medical News

early one-quarter of *Klebsiella pneumoniae* cultures in a network of U.S. long-term acute care hospitals are resistant to carbapenem, according to Jennifer H. Han, MD, and her associates.

From a sample of 3,846 *K. pneumoniae* cultures taken from 64 long-term acute care hospitals in 16 states, 946, or 24.6%, of the cultures were carbapenem-resistant, and were taken from 821 patients. Just under 54% of CRKP isolates were taken from a respiratory source, with 37% coming from urine and the remaining 9.4% coming from blood. Nearly all CRKP isolates were resistant to fluoroquinolones, and 59.2% were resistant to amikacin.

Respiratory failure was the most common comorbidity, occurring in nearly 40% of patients with CRKP. Just over 50% of CRKP patients had a central venous catheter, and 64.8% of patients had a tracheostomy. The median age of patients with CRKP was 72.

Of the 16 states from which cultures were taken, California had the highest rate of carbapenem resistance, with 45.5% of *K. pneumoniae* cultures showing resistance. Other states with high rates of CRKP included South Carolina, Kentucky, and Indiana.

"Given the chronically, critically ill population, with convergence of atrisk patients from multiple facilities, future studies of optimal infection prevention strategies are urgently needed for this setting. In addition, expansion of national surveillance efforts and improved communication between [long-term acute care hospitals] and acute care hospitals will be critical for reducing the continued emergence and dissemination of CRKP across the health care continuum," Dr. Han and her associates concluded.

Find the full study in Clinical Infectious Diseases (doi: 10.1 LTACHs 093/cid/ciw856).

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a median of 20 days off the ventilator, compared with 18 days for controls (P = .20), the investigators reported. However, dexmedetomidine led to significantly higher rates of well-controlled sedation. The highest rate of well-controlled sedation (defined as having a RASS scores between -3 and 1 throughout 1 day in the ICU) in treated patients was 58%, while the highest rate of well-controlled sedation in the control group was 39% (P = .01). Rates of adverse events did not significantly differ between groups. Bradycardia was most common, affecting 7% of the intervention group and 2% of controls (P = .1) the researchers said.

Hospira Japan provided partial funding with a grant to Wakayama Medical University, and helped design the study but was otherwise not involved in the research project. Dr. Kawazoe disclosed ties to Hospira Japan and Pfizer Japan. Three coinvestigators disclosed ties to Pfizer Japan, AbbVie, AstraZeneca, Daiichi Sankyo, and several other pharmaceutical companies. The other coinvestigators had no disclosures.

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### Some abnormal findings may be underemphasized

**BY JENNIE SMITH** Frontline Medical News

FROM CHEST

reporting system for lung cancer screening with low-dose computed tomography may underemphasize important abnormal findings other than nodules, researchers say, potentially leading to missed malignancies.

The American College of Radiology Lung Imaging Reporting and Data System, or Lung-RADS, was introduced in 2014 to standardize reporting for low-dose CT findings and also to reduce false-positive rates, by applying tighter criteria that was used in the National Lung Screening Trial.

Lung-RADS does not have specific reporting categories for patients with isolated hilar and mediastinal adenopathy or pleural effusion in the absence of lung nodules, even though these can indicate malignancy. It does allow for the inclusion of what is called an "S" code to indicate clinically significant findings other than nodules.

In the March 2017 issue of CHEST, Hiren Mehta, MD, and his colleagues at the University of Florida in Gainesville, report on four cases from their center in which patients with these pathologies had their scans read as Lung-RADS category 1, indicating a less than 1% likelihood of malignancy. No S codes were added to their reports. Subsequent testing in these patients revealed cancers (CHEST. 2017 March;151[3]:525-26).

The four cases were:

• A 56-year-old male with hilar and

mediastinal adenopathy who was recommended for repeat screening at 12 months. The patient presented 6 months later with pneumonia; biopsy revealed large cell lung cancer.

- A 76-year-old male with paratracheal lymph nodes and a solitary subcarinal lymph node. A subsequent biopsy revealed adenocarcinoma.
- A 67-year-old male whose scan showed bulky hilar and mediastinal adenopathy. Subsequent testing revealed Hodgkin's lymphoma.
- A 75-year-old female whose scan showed a small pleural effusion and no nodules. Repeat scanning at 1 year showed enlargement of the effusion and lung adenocarcinoma.

Dr. Mehta and colleagues noted in their analysis that Lung-RADS has not been studied prospectively in real practice settings and that the four cases – two of which involved delayed diagnosis – reveal "a significant limitation" of Lung-RADS.

"Based on our experience, we believe that particular caution should be exercised in reporting Lung-RADS 1 category for patients with adenopathy/pleural effusion with no lung nodules, as a majority of the lung cancer screening scans will be ordered by [primary care providers. As] with any new system, an ongoing evaluation of the performance of Lung-RADS should be conducted so that the sensitivity and mortality benefit seen in the [National Lung Screening Trial] is not compromised.

"We strongly believe, based on our experience with these 4 cases that

the new version of Lung-RADS 2.0 should [account for shortcomings of the current Lung-RADS] and have a separate category for findings that are highly suspicious for malignancy

### VIEW ON THE NEWS

M. Patricia Rivera, MD, FCCP, comments: The authors are commended for reporting these four cases as they highlight potential

pitfalls in lung cancer screening. However, while Lung-RADS reporting emphasizes lung nodules, it recognizes that intra and extrathoracic incidental findings are equally important and these findings should be assigned the letter S to the final interpretation. The

cases reported in this article should have been assigned a Lung-RADS 1S on the initial low-dose CT with recommendations from the reporting radiologist on management of the S findings. As highlighted by these cases, non-small cell lung cancer and lymphoma explained the nodes and pleural effusion. We must not forget that small cell lung cancer, comprising about 15% of all lung cancers, is not likely to present with a pulmonary nodule but rather with hilar and mediastinal adenopathy. We are not accustomed to diagnosing small cell lung cancer in early stages but one has to consider that this tumor may present early on with isolated

but do not have an accompanying lung nodule," they wrote.

The investigators did not disclose outside funding or conflicts of interest related to their findings.

hilar or mediastinal node.

Interpretation of a LDCT scan should follow the same practice as interpretation of CT scans outside



of screening, that is thorough evaluation for potential significant findings such as coronary artery calcifications, adrenal or renal lesions, effusion(s), ascites, adenopathy, etc. Furthermore, in the final interpretation of these scans, these findings should be clearly stated with recommenda-

tions for follow-up.

This report also highlights, in my opinion, the important responsibility of individual review of the LDCT by the provider(s) participating in a screening program. This, of course, may be more feasible for pulmonologists and surgeons who should have experience, gained through clinical practice, in interpretation of CT scans. Internists and primary care physicians who order LDCT most likely solely rely on the radiologist interpretation and recommendations, further highlighting the importance of accurate reporting with clear recommendations for follow-up not only of nodules but of incidental findings.

### Spread through air spaces portends lung SCC recurrence

#### BY RICHARD MARK KIRKNER Frontline Medical News

irst described in 2015, tumor spread through air spaces is a recently recognized form of invasion in lung carcinoma, but it has not been well described in lung squamous cell carcinoma. However, a study out of Memorial Sloan-Kettering Cancer Center reports spread through air spaces (STAS) is one of the most significant histologic findings in lung squamous cell carcinoma (SCC).

In multivariable models for any recurrence and lung cancer–specific death, the researchers found that STAS was a significant independent predictor for both outcomes (P = .034 and .016, respectively).

"We found that STAS in lung SCC was associated with p-stage, lymphatic and vascular invasion, necrosis, larger nuclear diameter, increased mitoses and high Ki-67 labeling index," wrote lead author *Continued on following page* 

### **VIEW ON THE NEWS**

### Refining prognosis with careful exam

**S** TAS (spread through air spaces) has emerged as a harbinger of poor clinical behavior in adenocarcinoma of the lung. In this new manuscript, a team from Memorial Sloan-Kettering Cancer Center demonstrates that this phenomenon is evident in squamous cell cancer of the lung as well.

A few important take-home messages are worthy of particular note in this manuscript. The first is that STAS is fairly common, present in onethird of all patients with squamous cell cancer. The second is that STAS is correlated with other known indicators of aggressive behavior such as stage, vascular and lymphatic invasion, and a high Ki-67 labeling index. The third is that STAS is not restricted to one particular histological subtype of squamous cell cancer. The fourth is that STAS is predictive of lung cancer–related recurrence and death, independent of other prognostic factors.

While the study needs to be replicated in other datasets, it demonstrates the power of careful pathologic examination in predicting tumor biology. The age-old concept deserves renewed emphasis in the current era of "Omics" of various kinds.

Sai Yendamuri, MD, is professor and chair of the department of thoracic surgery at Roswell Park Cancer Institute in Buffalo, N.Y., and is an associate medical editor for Thoracic Surgery News. He has no relevant disclosures.

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Shaohua Lu, MD, and coauthors (J Thorac Oncol. 2017 Feb;12[2]:223-34). Their findings are based on an analysis of 445 patients who had resection for stage I-III SCC over a 10-year period ending in 2009.

The Sloan-Kettering Group previously reported that STAS was a predictor of recurrence in stage I lung adenocarcinoma patients who had a limited resection (J Thorac Oncol. 2015;10[5]:806-14), and others reported STAS was a clinically significant finding in the disease. In the latest study, Dr. Lu and colleagues set out to determine if STAS is associated with tumor aggressiveness in lung SCC by using a large cohort of patients who had lung SCC resection. The lung resections they studied are from the aforementioned 2015 study that used immunohistochemistry to confirm squamous differentiation in otherwise poorly differentiated tumors.

Two pathologists reviewed tumor slides and used Ki-67 staining to confirm squamous differentiation. The study population comprised 98% former smokers, and the median age was 71.3; 76% (336) were older than 65.

Dr. Lu and colleagues noted how STAS in lung SCC differs from its presentation in lung adenocarcinoma. "In contrast to lung adenocarcinoma, in which STAS can manifest as micropapillary clusters, solid nests or single cells, all STAS lesions in lung SCCs consist of solid tumor cell nests," they wrote.

They found that STAS was associated with a higher risk of recurrence in SCC patients who had lobectomy, but not sublobar resection, whereas in patients with lung adenocarcinoma STAS was associated with a high risk of recurrence if they had sublobar resection.

The study observed STAS in 132 patients (30%). With a median follow-up of 3.4 years, 61% (273) of all patients died in that time. STAS tumors were more aggressive in nature than were non-STAS tumors. Pathologic features strongly associated with STAS were lymphatic invasion (40% for STAS vs. 19% for non-STAS patients); vascular invasion (36% vs. 22%); larger tumor size (median 4 cm vs. 3 cm); higher Ki-67 labeling index (32% vs. 13%); and higher tumor stage (23% with p-stage I, 35% p-stage II, and 43% p-stage III), all significant differences. Patients with STAS also had a higher 5-year cumulative incidence of any recurrence (39% vs. 26%) and lung cancer-specific death (30% vs. 14%), both significant differences.

STAS has an "insidious pattern of tumor invasion" that can be difficult for pathologists to detect and requires the gathering of specimens that include the adjacent lung parenchyma, Dr. Lu and colleagues said. They also dispelled the myth that STAS is an ex vivo artifact. "STAS is morphologically different from tissue floaters and contaminant or extraneous tissues that can lead to diagnostic errors," they said.

And while the study showed that STAS is an independent predictor of recurrence and cancer-specific death, it was not predictive of overall survival – perhaps because most of the study population was over age 65 and were more likely to die from other causes rather than lung cancer. "We found a strong correlation between STAS and highgrade morphologic patterns such as nuclear size, nuclear atypia, mitotic count and Ki-67 labeling index, suggesting that STAS is associated with tumor proliferation," Dr. Lu and coauthors said.

"Because we found STAS to show greater prognostic significance than lymphatic vascular and visceral pleural invasion," it may be appropriate for STAS to be recorded for lung cancer specimens in pathology reports, the researchers noted.

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### **EBUS** scope, EUS-FNA similarly effective

BY DEEPAK CHITNIS Frontline Medical News

n an assessment of a patient for lung cancer, a procedure involving the insertion of an EBUS scope in the esophagus – EUS-B-FNA – can achieve similarly accurate results as endoscopic ultrasound guided– fine-needle aspiration (EUS-FNA), according to a new study.

This finding could lead patients to

choose EUS-B-FNA over EUS-FNA – the standard of care for analyzing potential metastasis of the left adrenal glands (LAGs) – resulting in both time and cost savings for patients. The current standard of care involves using an EBUS scope for complete mediastinal and hilar staging of lung cancer or, if present, a tumor. This is then followed by an assessment of the LAG by conducting ultrasound guided—fine-needle aspiration with a

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different scope. However, in this study, the investigators included an experimental procedure between those two steps, which involved advancing the EBUS scope into the patients' stomachs to find and assess the LAG. The idea is that, by using just one tool and technique rather than using an EBUS scope followed by the traditional EUS- FNA (which involves using a second scope), both the patient and the provider save time and money.

"A recent report showed that LAG visualization using the EBUS scope was possible in 85% of patients," according to the authors of this study, including Jouke T. Annema, MD, of the University of Amsterdam. Prior to this new research, it was unknown to what extent a single EBUS scope adequately assess and sample the LAGs and how its performance related to the use of a conventional endoscopic ultrasound– guided scope (Lung Cancer. 2017. doi: org/10.1016/j.lungcan.2017.02.011).

Dr. Annema and his coauthors recruited patients from four centers

three in the Netherlands, one in Poland – and followed them prospectively.
 Patients with "(suspected) lung cancer [who] had an indication for both mediastinal lymph node and LAG sampling" were recruited for the study. The researchers followed 44 patients through final diagnosis to determine if they *Continued on following page*

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### **Sected** The Newsard of the American College of Chest Physician

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ultimately had lung cancer.

Subjects first received complete mediastinal and hilar staging of lung cancer and any present tumors via an EBUS and EUS-B procedure. Following an EBUS examination of the mediastinum, the EBUS scope was retracted from the trachea and positioned into the esophagus for an examination of the mediastinal nodes. Then, the EBUS scope was advanced into the stomach for identification of the LAG. Afterward, the routine EUS-FNA was performed. LAG analysis across both methods involved visualizing the LAG and collecting an adequate tissue sample for testing.

"In short, in order to locate the LAG, a structured three step approach was used according to the EUS assessment tool (EUS-AT): identification of the liver, abdominal aorta, coeliac trunk, left kidney, and LAG," the authors noted. "By turning the EBUS scope clockwise from the liver, the abdominal aorta and coeliac trun[k] are identified. By subsequently turning the EBUS scope gently in caudal direction, the left kidney and LAG are identified."

Endoscopists then evaluated both procedures in each subject according to feasibility and practicability to determine if the findings of the experimental procedure were us-

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able. Finally, a cytologic exam was conducted, using Giemsa or Papanicolaou staining to determine if any present cancer had metastasized, and a final diagnosis was made.

LAG analysis had a success rate of 89% (39/44; 95% confidence interval, 76%-95%) for EUS-B-FNA, compared with 93% (41/44; 95% CI, 82%-98%) for EUS-FNA. Similarly, when looking at the rate of sensitivity for LAG metastases, EUS-B had a rate of sensitivity for LAG metastases of at least 87% (95% CI, 65%-97%), while EUS-FNA was found to be at least 83% (95% CI, 62%-95%. Endoscopists were equally satisfied with both procedures in the "majority" of cases in this study. "In [five] cases (11%), the EUS-B-FNA procedure was unsuccessful, due to the inability to make good contact of the ultrasound transducer and the stomach wall," the authors explained. "The conventional EUS scope is more stable as a result of the increased tube diameter. Another advantage of the conventional echo-endoscope is its

wider scanning angle. ... The conventional EUS scope is also longer than the EBUS scope, [but that] does not seem to be the limiting factor."

No funding source was disclosed for this study. The authors reported no relevant financial disclosures.

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### Lung cancer screening a challenge to implement

**BY JENNIE SMITH** Frontline Medical News

comprehensive lung cancer screening program carried out at Veterans Health Administration hospitals was taxing to implement and revealed a large number of patients with results requiring follow-up, though only 1.5% had cancers.

Investigators at eight VHA hospi-

tals, led by Linda S. Kinsinger, MD, of the VHA's National Center for Health Promotion and Disease Prevention in Durham, N.C., looked at records from about 93,000 primary care patients and identified 4,246 eligible for screen-

### ing, based on age, medical history, and smoking history (JAMA Intern Med. 2017 Jan 30. doi: 10.1001/jamainternmed.2016.9022).

Approximately 58% of the eligible patients consented, and 2,106 underwent screening with low-dose computed tomography (LDCT) scans. The mean age of patients was 65 years, and 96% of patients were male. Nearly 60% of patients screened (1,257) had nodules, 1,184 patients (56.2%) required tracking, and 31 patients (1.5%) had lung cancer. The pilot study was developed in response to a 2013 recommendation from the U.S. Preventive Services Task Force favoring annual screening with LDCT scans in current or former heavy smokers between 55 and 80 years old. The recommendation sparked concerns about the practicability of implementing large-scale lung cancer screening, which Dr. Kinsinger and her colleagues' study seemed to underscore. For example, "creating electronic tools to capture the necessary clinical data in real time ... proved to be difficult, even with the VHA's highly regarded electronic medical record," the investigators wrote. A key measure used in the screening program - cigarette pack-years - was "not fully captured" in the system's EMR.

The investigators also noted that, if the eligibility criteria used in the pilot program were applied to the VHA nationwide, about 900,000 patients would be eligible for LDCT scan screening, and that fewer than 60% of patients in this study had consented. That meant that "accurately identifying these patients and discussing with them the benefits and harms of [screening] will take significant effort for primary care teams." Additionally, the required follow-up "may stress the capacity" of radiology and pulmonology services, they said. Finally, "primary care will need to be involved in deciding which incidental findings need further evaluation. These clinical efforts will require coordination and communication among clinical services and between patients and staff, and dedicated coordinators will need to be hired," the investigators said.

The authors noted that their findings might not be generalizable to non-VHA health care systems. The experience of the VHA, "owing to its central organizational structure, may represent a best-case scenario," they wrote.

The Veterans Health Administration funded the study. Two of its coauthors reported commercial conflicts of interest; one of those disclosed a grant application to the Bristol-Myers Squibb Foundation related to the screening.

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### Bill would limit noneconomic damages to \$250,000

BY ALICIA GALLEGOS Frontline Medical News

ew legislation headed to the House floor could mean legal relief for health providers in the form of capped damages and a tighter time frame for lawsuits.

The House Judiciary Committee passed the Protecting Access to Care Act of 2017 (H.R. 1215) in February by a vote of 18-17. The bill, modeled after California's Medical Injury Compensation Reform Act (MICRA), would limit noneconomic damages in medical malpractice cases to \$250,000, restrict contingency fees charged by attorneys, and enforce a 3-year statute of limitations for liability lawsuits from the date of alleged injury. The bill also includes a "fair share" rule in which defendants are liable only for the damages in direct proportion to their percentage of responsibility.

The bill is the first significant medical professional liability reform legislation to be approved by the committee since 2011, said Brian K. Atchinson, president and CEO of PIAA, a national trade association for medical liability insurers.

"Unlike previous federal bills, the bill is focused solely on health care professionals and entities, includes detailed flexibility for states for all its reforms, and is linked with the expenditure of federal dollars to address states' rights concerns," Mr. Atchinson said in a statement. "H.R. 1215 will help ensure fair and timely compensation to injured patients, improve access to patient care, and promote affordable and accessible medical liability insurance coverage."

The proposed statute would apply to any patient who receives medical care provided via a federal

program, such as Medicare or Medicaid, or via a subsidy or tax benefit, such as coverage purchased under the Affordable Care Act or a future replacement. Medical care paid by employer health plans would fall under the legislation's umbrella since

insurance premiums receive federal tax exemptions. The bill would not preempt state medical malpractice laws that impose damage caps, whether higher or lower than \$250,000, nor would the legislation affect the availability of economic damages, according to bill language.

As part of the H.R. 1215, courts could limit how much

attorneys receive from a patient's ultimate award. Specifically, courts would have the power to restrict payments from a plaintiff's damage recovery to an attorney who claims a financial stake in the outcome by virtue of a contingent fee.

If enacted, the bill would work to reduce the practice of defensive medicine and save taxpayer dollars, while increasing access to health care, said House Judiciary Committee Chair Bob Goodlatte (R-Va.).

'The Protecting Access to Care Act will help keep the rising costs of health care from being passed along to the American people," Rep. Goodlatte said in a statement. "The Congressional Budget Office estimates that the reforms contained in the bill would lower health care costs by tens of billions of dollars."

Public Citizen, a consumer rights group, criti-



**REP. GOODLATTE** 

cized the legislation as misleading to consumers and harmful to patients.

"Proposals to shield providers from liability are nothing but a giveaway to industry," Lisa Gilbert, director of Public Citizen's Congress Watch, said

> in a statement. "Members supporting this bill would further harm those who are suffering from doctors' mistakes and abandon the GOP's supposedly unwavering commitment to state's rights.'

Jeffrey Segal, MD, a neurosurgeon and attorney, said the bill faces an uphill climb and may not make it very far. The question is whether the

legislation can pass via the budget reconciliation process (requiring only a simple majority in the Senate) or whether it would be presented outside of that process and would need 60 votes, he said in an interview.

"There are so many moving parts to this bill, I think the likelihood of its being passed as is is low," said Dr. Segal, founder of Medical Justice, a company that works to deter frivolous medical malpractice lawsuits. "The biggest challenge will be whether the Republicans have to get eight Democratic senators to join the bill. To make it more palatable, something will need to give. Such provisions on tort reform are likely to be the first items offered for sacrifice."

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# DR. SEGAL

House leaders 'came up short' in effort to kill Obamacare

### BY MARY AGNES CAREY, KAISER HEALTH NEWS

espite days of intense negotiations and last-minute concessions to win over wavering GOP conservatives and moderates, House Republican leaders failed to secure enough support to pass their plan to repeal and replace the Affordable Care Act.

House Speaker Paul Ryan pulled the bill from consideration after he rushed to the White House to tell President Donald Trump that there weren't the 216 votes necessary for passage.

"We came really close today, but we came up short," he told reporters at a hastily called news conference.

When pressed about what happens to the federal health law, he added, "Obamacare is the law of the land.

... We're going to be living with Obamacare for the foreseeable future."

President Trump laid the blame at the feet of Democrats, complaining that not one was willing to help

Republicans on the measure, and he warned again that the Obamacare

insurance markets are in serious danger. "Bad things are going to happen to Obamacare," he told reporters at the White House. "There's not much you can do to help it. I've been saying that for a year and a half. I said, look, eventually, it's not sustainable. The insurance companies are leaving."

But he said the collapse of the bill might allow Republicans and Democrats to work on a replacement. "I honestly believe the Democrats will come to us and say, 'Look, let's get together and get a great health care bill or plan that's really great for the people of our country," he said.

Rep. Ryan originally had hoped to hold a floor vote on the measure March 23 – timed to coincide with the 7th anniversary of the ACA – but decided to delay that effort because GOP leaders didn't have enough "yes" votes. The House was in session March 24. before his announcement, while members debated the bill.

House Democratic leader Nancy Pelosi (Calif.) said the speaker's decision to pull the bill "is pretty exciting for us ... a victory for the Affordable Care Act, more importantly for the American people."

The legislation was damaged by a variety of issues raised by competing factions of the party. Many members were nervous about reports by the Congressional Budget Office showing that the bill would lead eventually to 24 million people losing insurance, while some moderate Republicans worried that ending the ACA's Medicaid expansion would hurt low-income Americans.

At the same time, conservatives, especially the hard-right House Freedom Caucus that often has needled party leaders, complained that the bill kept too much of the ACA structure in place. They wanted a straight repeal of Obamacare, but party leaders said that couldn't pass the Senate, where Republicans don't have enough votes to stop a filibuster. They were hoping to use a complicated legislative strategy called budget reconciliation that would allow

them to repeal parts of the ACA that affect only federal spending.

The decision came after a chaotic week of negotiations, as party leaders sought to woo more conservatives. The president lobbied 120 members through personal meetings or phone calls, according to a count provided by his spokesman, Sean Spicer. "The president and the team here have left everything on the field," Mr. Spicer said.

On the evening of March 23, Mr. Trump dispatched Office of Management and Budget Director Mick Mulvaney to tell his former House GOP colleagues that the president wanted a vote on March 24. It was time to move on to other priorities, including tax reform, he told House Republicans.

"He said the president needs this; the president has said he wants a vote tomorrow, up or down. If for any reason it goes down, we're just going to move forward with additional parts of his agenda. This is our Continued on page 36

### **36 PRACTICE ECONOMICS**

Continued from page 31

moment in time," Rep. Chris Collins (R-N.Y.), a loyal Trump ally, told reporters late on March 23. "If it doesn't pass, we're moving beyond health care. ... We are done negotiating."

Trump's edict clearly irked some lawmakers, including the Freedom Caucus chairman, Rep. Mark Meadows (R-N.C), whose group of more than two dozen members represented the strongest bloc against the measure.

"Anytime you don't have 216 votes, negotiations are not totally over," he told reporters who had surrounded him in a Capitol basement hallway as he headed in to the party's caucus meeting.

President Trump, Speaker Ryan, and other GOP lawmakers tweaked their initial package in a variety of ways to win over both conservatives and moderates. But every time one change was made to win votes in one camp, it repelled support in another.

The White House on March 23 accepted conservatives' demands that the legislation strip federal guarantees of essential health benefits from insurance policies. But that was another problem for moderates, and Democrats suggested the provision would not survive in the Senate.



Republican moderates in the House – as well as the Senate – objected to the bill's provisions that would shift Medicaid from an open-ended entitlement to a set amount of funding for states that also would give governors and state lawmakers more flexibility over the program. Moderates also were concerned that the package's tax credits would not be generous enough to help older Americans – who could be charged five times more for coverage than would their younger counterparts – afford coverage.

The House package also lost the support of key GOP allies, including the Club for Growth and Heritage Action. Physician, patient, and hospital groups also opposed it.

But Rep. Ryan's comments made clear how difficult this decision was.

"This is a disappointing day for us," he said. "Doing big things is hard. All of us. All of us – myself included – we will need time to reflect on how we got to this moment, what we could have done to do it better."

Kaiser Health News is a national health policy news service that is part of the nonpartisan Henry J. Kaiser Family Foundation.



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# Hospitalizations fell after rotavirus vaccine, PCVs

BY DAN WATSON Frontline Medical News

accination programs targeting rotavirus and pneumonia in children younger than 2 years both contributed to a "rapid and considerable" decline in the hospital burden of pediatric patients, both in relation to those diseases and overall, according to an observational study.

Three vaccines were added to the National Immunization Plan in Israel within a 1.5-year interval, between July 2009 and January 2011: rotavirus vaccine and the 7-valent and 13-valent pneumococcal conjugate vaccines (PCV). Researchers studied the population at the Soroka University Medical Center in Beer Sheva, Israel, which was split roughly 50/50 between Jewish children and Bedouin Muslim children.

"The socioeconomic conditions and lifestyles of the two populations differ and social contacts between them, especially between children, are uncommon. However, both have access to the same medical services," wrote Shalom Ben-Shimol, MD, of Ben-Gurion University of the Negev, Beer Sheva, and coauthors (J Pediatr. 2017 Mar;182:253-9.e2).

The rates of rotavirus gastroenteritis, nonrotavirus gastroenteritis, alveolar pneumonia, and nonalveolar lower respiratory tract infections in the 37,591 hospitalized children younger than 2 years declined by 78%, 21%, 46%, and 7%, respectively, over the course of the study period. Outpatient ED visits for the same diseases declined 80%, 16%, 67%, and 13%, respectively.

The results are more evidence that rotavirus vaccine can help prevent diarrhea not caused by rotavirus and, similarly, that PCV can help

**VIEW ON THE NEWS** 

Susan Millard, MD, FCCP,

**comments:** These two articles

represent the importance of vac-

cinations and their impact on the

health of children worldwide. It

is important to advocate locally

and on a national level, no mat-

ter what the political climate is,

for improvement in vaccination

rates and vaccine research.

prevent lower respiratory tract infections not caused by pneumococci.

Overall, hospitalizations and outpatient ED visits also declined significantly, by 11% and 12%, respectively. "The impact

of [rotavirus vaccine] and PCV

may not be limited to prevention of diarrhea and respiratory disease, respectively. In one study, it was suggested that diarrhea may increase the risk of subsequent pneumonia in young children, pointing to potential synergistic benefits" of the vaccines, the authors wrote (Am J Epidemiol. 2005;162[10]:999-1007).

The study was supported by Merck Sharp & Dohme and Pfizer. Authors received speaker fees, research support, and consulting fees from those companies and from GlaxoSmithKline.

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# Unvaccinated first hit in pertussis outbreak

BY LUCAS FRANKI Frontline Medical News

uring a 2012 pertussis outbreak in Oregon, unvaccinated or poorly vaccinated children were affected significantly earlier than fully vaccinated children were, according to Steve G. Robison, MPH, and

> Juventila Liko, MD, MPH, from the Immunization Program, Oregon Health Authority, Portland.

A total of 351 pertussis cases in children aged 2 months to 10 years were reported in Portland and the upper Willamette Valley from Jan.

1 to Nov. 1, 2012. Children who were unvaccinated accounted for 76 (22%) of the reported cases, and children who were poorly vaccinated accounted for 50 of the 275 (18%) cases in vaccinated children.

The median date of onset for unvaccinated and poorly vaccinated children was 117 days after Jan. 1, and the median date of onset for fully vaccinated children was 158 days after Jan. 1. Mean date of onset was 133 days and 159 days after Jan. 1, respectively. In zip codes with both unvaccinated and vaccinated cases, children who were unvaccinated were 3.2 times more likely to have an earlier onset date.

"Diseases such as pertussis may spread across areas through the choice of parents to not immunize or to limit immunizations. Once locally present, pertussis will spread to the unimmunized and vulnerable, who in turn through the weight of exposure, may then ignite a wider outbreak in vaccinated populations," the investigators noted.

Find the full study in the Journal of Pediatrics (doi: 10.1016/j. jpeds.2016.12.047).

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# Pneumococcal conjugate vaccine resulted in a 95% decline in *Streptococcus pneumoniae* bacteremia

**BY HEIDI SPLETE** Frontline Medical News

Routine use of the 13-valent pneumococcal conjugate vaccine (PCV13) reduced the incidence of *Streptococcus pneumoniae* bacteremia by 95% from a time period before to a time period after the vaccine was implemented, based on a review of more than 57,000 blood cultures from children aged 3-36 months.

Kaiser Permanente implemented universal immunization with PCV13 in June 2010. "Initial trends through 2012 demonstrated continued decline in pneumococcal infections, with the biggest impact in children less than 5 years old," wrote Tara Greenhow, MD, of Kaiser Permanente Northern California, San Francisco, and her colleagues.

The researchers conducted a retrospective cohort study of 57,733 blood cultures collected between Sept. 1, 1998, and Aug. 31, 2014, from previously healthy children aged 3-36 months seen in a single emergency department (Pediatrics. 2017 Mar 10. doi: 10.1542/peds.2016-2098).

Overall, the incidence of *S. pneumoniae* bacteremia declined from 74.5 per 100,000 children during the period before PCV7 (1998-1999) to 3.5 per 100,000 children during a period after routine use of PCV13 (2013-2014). The annual number of bacteremia cases from any cause dropped by 78% between these two time periods.

As bacteremia caused by pneumococci decreased, 77% of cases in the post-PCV13 time period were caused by *Escherichia coli, Salmonella spp.*, and *Staphylococcus aureus.* "A total of 76% of bacteremia occurred with a source, including 34% urinary tract infections, 17% gastroenteritis, 8% pneumonias, 8% osteomyelitis, 6% skin and soft tissue infections, and 3% other," Dr. Greenhow and her associates reported.

The large population of the Kaiser Permanente system supports the accuracy of the now rare incidence of bacteremia in young children, the researchers noted. However, "because *bacteremia* in the post-PCV13 era is more likely to occur with a source, a focused examination should be performed and appropriate studies should be obtained at the time of a blood culture collection," they said.

### **CRITICAL CARE COMMENTARY:** Sepsis resuscitation in a post-EGDT age

BY LYNDSAY W. HEAD, MD, AND CRAIG M. COOPERSMITH, MD

ritical care – like all of medicine – is evolving at a rapid pace. In the relatively recent past, we moved from an era of consensus-based (if thinking optimistically) or opinion-based (if being less charitable) medicine to an era of evidence-based medicine. Despite the many valid concerns about ubiquitous adoption of



evidence-based medicine, there is little doubt that, on average, an aggregate population managed according to the best available literature does better than



to the best available literature does better than one managed solely on widely varying physician expertise. At the same time, there is no doubt that one size does not fit all, and in applying evidence-based protocols to all patients equally,

**DR. COOPERSMITH** 

we are helping many, having no effect on many, and are harming some. This has led to a still ongoing transition into an era of precision medicine where each patient gets the best care specifically for them. While the intellectual appeal of personalized therapy is obviously immense, the tools with which to do so currently remain relatively limited.

The approach to sepsis resuscitation is emblematic of the challenges and opportunities of the evolution in this transition. There was no standardized approach to early sepsis resuscitation in the 20th century, and mortality from the disease approached 50% in many studies. This changed in 2001 with the publication of the landmark early-goal-directed therapy (EGDT) trial (Rivers et al. N Engl J Med. 2001;345[19]:1368). This single center trial demonstrated a dramatic 16% absolute decrease in mortality secondary to usage of an aggressive protocol for sepsis resuscitation within the first 6 hours after presentation to the ED. In addition to early cultures and antibiotic therapy in patients randomized to both EGDT and "usual care," EGDT involved a number of mandatory elements, including placing both an arterial catheter and a central venous

catheter capable of measuring continuous central venous oxygen saturation  $(ScvO_2)$ . Patients received crystalloid or colloid until a predetermined central venous pressure was obtained, and if their mean arterial pressure was still below 65 mm Hg, therapy with pressors was initiated. If their ScvO<sub>2</sub> was not 70% or greater, patients were transfused until their hematocrit was greater than 30%, and, if this still did not bring their ScvO<sub>2</sub> up, patients

were started on a regimen of dobutamine. Multiple trials of varying design subsequently demonstrated efficacy in this approach, which was rapidly adopted worldwide in many centers managing patients with sepsis.

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### NEWS FROM CHEST 39

However, many questions remained. All patients were managed the same in EGDT, with no capacity to individualize care, regardless of clinical situation (comorbidities, age, origin of sepsis). In addition, it was never clear which specific elements of the EGDT protocol were responsible for its success, as a bundled protocol could potentially simultaneously include beneficial, harmful, and neutral components. Further, many of the elements of EGDT have not been demonstrated to be beneficial in isolation. For example, multiple studies demonstrate that patients not receiving transfusions until their hemoglobin value reaches 7 g/dL is at least as effective as receiving transfusions to a hemoglobin value of 10 g/dL. Also, there is a wealth of data suggesting that central venous pressure is not an accurate surrogate for intravascular volume.

To address these issues, three international, multicentered randomized controlled trials were published in the *New England Journal of Medicine*  in 2014 and 2015: ARISE, ProCESS, and ProMISe (ARISE investigators. *N Engl J Med.* 2014;371[16]:1496; ProCESS investigators. *N Engl J Med.* 2014;370[18]:1683; Mouncey, et al. *N Engl J Med.* 2015;372[14]:1301). Each of these studies randomized patients either to EGDT as defined in the orig-*Continued on following page* 

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### 40 NEWS FROM CHES1

#### Continued from previous page

inal Rivers study or to a "usual care" group with management directed under the guidance of a bedside healthcare provider. Across all three trials, the EGDT group received more fluids, inotropes, vasopressors, and transfusions than the" usual care" group. However, there was no mortality benefit detected in any of the trials.

The difference between the original Rivers trial (demonstrating a huge benefit of EGDT) and the three subsequent trials leads (showing no benefit) was striking and leads to the obvious questions of (a) why were the results so disparate and (b) what should we do for our patients moving forward? Perhaps the most obvious difference in the trials is the baseline mortality in the "usual care" groups between the studies. In the original Rivers study, in-hospital mortality was 46.5% for the "usual care" group. For ARISE, ProCESS, and ProMISe, 60- to 90-day mortality ranged from 18.8% to 29.2%

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in the "usual care" group. This means either that the patients in the original EGDT trial were significantly sicker or that something fundamental has changed over time. A closer review of the papers reveals it is likely the latter as, in actuality, the "usual care" group in the three NEJM trials looked a lot like the EGDT group in the original trial. Most patients received significant volume resuscitation in these studies prior to enrollment, and the original ScvO<sub>2</sub> was 71% in ProCESS (as opposed to 49% in the original Rivers trial). This suggested that increasing awareness of sepsis that occurred during the 15 years between the EGDT trial and the subsequent three trials - likely due to the Surviving Sepsis Campaign, as well as other efforts from both advocacy groups as well as medical organizations – led to better sepsis care on patient presentation. In essence, what was "usual care" in the time of the original EGDT study had become inappropriate care in the modern era, and much of what was protocolized in EGDT had been transformed into "usual care," even if a specific protocol was not being used. In the setting in which "usual care" had dramatically improved, the original EGDT protocol was not helpful if implemented on all comers. One key reason is that many patients simply improved with volume and antibiotics (which had become "usual care") and did not need additional interventions. Another reason is that some of the interventions in EGDT (blood transfusion, continuous ScvO<sub>2</sub> monitoring) are likely not beneficial in the majority of cases.

These studies have led to significant changes in recommendations in sepsis management guidelines. The 2016 Surviving Sepsis Campaign guidelines - published after ARISE, ProCESS and ProMISe trials - still recommend antibiotics, cultures, adequate volume resuscitation (without specifying how to do so), targeting an initial mean arterial pressure of 65 mm Hg, and vasopressors if a patient remains hypotensive despite adequate fluids (Rhodes et al. Crit Care Med. 2017; 45). However, no recommendations are made regarding mandatory placement of a central venous catheter, measuring central venous pressure, transfusing to higher hemoglobin, etc.

In many ways, the last 15 years of fluid resuscitation in sepsis represents the triumph of evidence-based medicine over opinion-based medicine and the challenges of moving toward precision medicine. When "usual care" was highly variable without a consistent scientific rationale, EGDT markedly improved outcomes – a clear victory of evidence-based medicine that likely saved thousands of lives. However, when EGDT effectively became "usual care," each individual element of EGDT bundled together failed to further improve outcome. The new evidence suggested that for all comers, EGDT is no better than the new normal, and, thus, newer guidelines do not recommend most of its components.

Moving forward, what is the best way to resuscitate newly identified patients with sepsis? A big fear in eliminating EGDT in its entirety is that practitioners will not have any guidance on how to manage resuscitation in sepsis and so will revert to less rigorous practice patterns. While we acknowledge that concern, we are optimistic that the future will continue to yield decreases in sepsis mortality. Optimally, volume status will be assessed on an individual basis. Rather than resuscitating every patient with a one-size-fits-all parameter that is fairly crude at best and inaccurate at worst (central venous pressure), bedside caregivers should use whatever tools are most appropriate to their individual patient and expertise. This could include bedside ultrasound, stroke volume variation, esophageal Doppler, passive leg raise, etc, depending on the clinical situation. The concept of appropriate volume resuscitation raised in EGDT continues to be 100% valid, but the implementation is now patient-specific and will vary upon available technology, provider skill, and bedside factors that might make one method superior to the other. Similarly, the failure of EGDT to improve survival in the ARISE, ProCESS, and ProMISe trials does not mean there is never a role for checking venous blood gases and measuring ScvO<sub>2</sub>. From our point of view, this would be a gross misinterpretation of the trials, as the finding that all elements of EGDT combined fail to benefit all patients with sepsis on arrival should assuredly not be interpreted as none of the elements of EGDT can ever be beneficial in any patients with sepsis. While we can - and should – learn from the data as they pertain

to "all comers," we equally can - and should - look at each individual patient and determine where they align with what is known (and unknown) in the literature and simultaneously attempt to both personalize and optimize their care utilizing our general knowledge of physiology and individual information that is unique to the patient.

In the future, we hope that sepsis resuscitation will be performed in an analogous fashion to cancer therapy. Understanding a patient's response at the organ level and cellular and subcellular levels will allow us to individualize initial therapy. For instance, an "omics" evaluation of a patient's immune system may be helpful for guiding treatment. Distinct patterns of gene and protein expression could potentially demonstrate in advance how different patients will respond differently to the same therapy and, in a dynamic manner, determine whether they are responding according to the expected trajectory. Unfortunately, since this is impractical today, the best we can do is to follow recommendations that are applicable to large populations (the Surviving Sepsis bundles) while simultaneously individualizing therapy when no clear data are available. Further, it is critical to assess and reassess the response at the bedside to optimize outcomes. While it is frustrating that no clear guidance can be given on the best way to measure volume status or fluid responsiveness or when there is utility in measuring ScvO<sub>2</sub>, there is comfort in knowing that best practice has evolved over the past 15 years such that the majority of EGDT is now "usual care." Moving forward, the challenges in transitioning sepsis resuscitation from population-based evidence-based medicine to individualized therapy are real, but the opportunities for improved outcomes in this deadly disease are enormous.

Dr. Head is with the Department of Anesthesiology, and Dr. Coopersmith is with the Department of Surgery, Emory Critical Care Center, Emory University School of Medicine, Atlanta, GA.

### **EDITOR'S NOTE**

e must admit that we are all imperfect beings and, as such, we are all incorrect from time to time. In order to evolve to proverbial 'higher planes of enlightenment,' we must accept our cognitive errors - sometimes as individuals and other times as a collective entity. Within this framework of improvement through critical reflection, evidence-based medicine has been born. In this commentary, the authors address an area of smoldering contention and conflicting evidence-the role of EGDT in managing sepsis. If their call for an individualized approach to therapy is ultimately the ideal strategy, it may vindicate us all by simultaneously proving us all wrong.

Lee E. Morrow, MD, FCCP

### In Memoriam

andra K. Willsie, DO, FCCP, died on March 26, 2017, after a courageous battle with brain cancer. As an osteopathic physician with board certification in internal medicine, pulmonary diseases, and critical care medicine, Sandra worked diligently for over 30 years to further scientific discovery and health-care education.

An NIH-funded career academic awardee, a Macy Institute scholar, and an invited faculty member on health-care leadership at Harvard University, Sandra was very involved in academic medicine. She served as professor of medicine, interim chair of medicine and docent at the University of Missouri–Kansas City School of Medicine; and as provost, dean, vice-dean, and department chair at Kansas City University of Osteopathic Medicine. Sandra earned a master's degree in bioethics and health policy focusing on research ethics from Loyola University of Chicago Stritch School of Medicine. She made countless scholarly presentations and published regularly.

Sandra made eight pro bono trips to provide physicians in Honduras,

Panama, Costa Rica, and the Dominican Republic the latest research updates on asthma and COPD research. She was honored to serve as president of Women Executives in Science and Healthcare and as board president of the American Heart Association's Midwest Affiliate. She had been volunteering for over 30 years at the KC CARE Clinic in downtown Kansas City, Missouri, and was a committee member of the FDA advisory panel on respiratory and anesthesiology devices.

Sandra devoted many years of active participation to the American College of Chest Physicians and will be missed by so many colleagues and friends. She served on the Board of Regents and on the US and Canadian Council of Governors, was a member of numerous committees, including Education, Ethics, Marketing, Nominating, and Chair of the Scientific Presentations and Awards Committee. A staunch supporter of the CHEST Foundation, she was instrumental in its creation and served as a board and committee member. We extend our heartfelt condolences to her husband, Tom, and her family and many friends.

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# **PULMONARY PERSPECTIVES**: Ensuring quality for EBUS bronchoscopy with varying levels of practitioner experience

BY AMIT K. MAHAJAN, MD, FCCP; SANDEEP J. KHANDHAR, MD; AND ERIK FOLCH, MD, MSC ness of EBUS-TBNA improves with increasing number of procedures performed, allowing for access to a greater number of lymph nodes with-

out necessarily increasing the length of the procedure, and by reducing the number of punctures at each nodal station. Based on their results, the first 20 procedures performed yielded a 70% accuracy, 21 to 40 procedures performed resulted in 81.8% accuracy, 41 to 60 procedures performed

ndobronchial ultrasound (EBUS) bronchoscopy is a tool that has transformed the diagnosis and staging of lung cancer. Through real-time ultrasound imaging, EBUS provides clear images of lymph nodes and proximal lung masses that can be adequately sampled through transbronchial needle aspiration. EBUS is a minimally invasive, outpatient procedure that can also be used for diagnosing benign disease within the chest. Large studies investigating the use of EBUS for mediastinal staging have shown the procedure to be highly sensitive and specific while harboring an excellent safety profile.<sup>1</sup> As a result, EBUS has essentially replaced mediastinoscopy for the staging of lung cancer.

EBUS bronchoscopy was primarily offered at major academic centers when first released and was performed by physicians who were formally trained in the procedure during interventional pulmonology or thoracic surgery fellowships. Over time, the tool has been adopted by established general pulmonologists without formal training in EBUS. Some of these pulmonologists only develop their skills by attending 1- to 2-day courses, which is insufficient supervision to become competent in this important procedure.

An ongoing debate continues as to how many supervised EBUS bronchoscopies should be performed prior to being considered proficient.<sup>2</sup> As procedural competence has been associated with the number of EBUS procedures performed, the learning curve required to master EBUS is an important component of proficiency. While most consider learning curves to be variable, evidence produced by Fernandez-Villar and colleagues revealed that EBUS performance continues to improve up to 120 procedures.<sup>3</sup> This analysis was performed in unselected consecutive patients based on diagnostic yield, procedure length, number of lymph nodes passes performed in order to obtain adequate samples, and the number of lymph nodes studied per patient. The learning curve was evaluated based on consecutive groups of 20 patients, the number of adequate samples obtained, and the diagnostic accuracy. Their results indicated that the diagnostic effectiveThis advertisement is not available for the digital edition.

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resulted in 83.3% accuracy, 61 to 80 procedures performed resulted in 89.8% accuracy, 81 to 100 procedures performed resulted in 90.5% accuracy, and 101 to 120 procedures performed resulted in 94.5% accuracy.

While the American Thoracic Society (ATS) and the American College of Chest Physicians (CHEST) both

recommend a minimum number of 40 to 50 supervised EBUS bronchoscopies prior to performing the procedure independently, along with 20 procedures per year for maintenance of competency, most institutions do not track the number of EBUS procedures performed and they do not follow the ATS or CHEST recommendations.<sup>4,5</sup> As a result, a number of physicians are independently performing EBUS without adequate experience, resulting in possibly poor quality care. Unfortunately, some short courses, intended to generate interest and encourage attendees to pursue further training, are mistakenly assumed to be sufficient by the novice user.

As the number of interventional pulmonary fellowships continues to expand, the growing number of subspecialized pulmonologists with extensive training in EBUS grows. During a dedicated interventional pulmonary fellowship, fellows perform well above the number of *Continued on following page* 

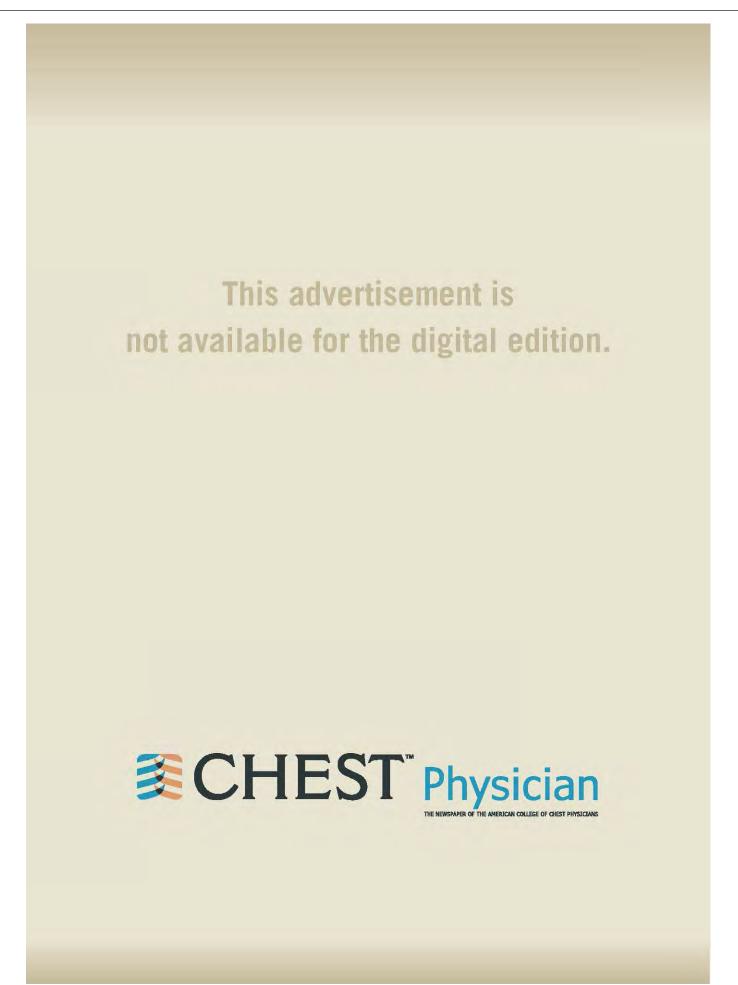
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EBUS bronchoscopies suggested by the ATS and CHEST in a single year. Recently published accreditation guidelines require a minimum of 100 cases per interventional pulmonary fellow.<sup>6</sup> These fellowship-trained interventional pulmonologists are then tested to become board-certified in a wide array of minimally invasive procedures, including EBUS. As a result, a model has developed where both board-certified interventional pulmonologists with extensive training in EBUS and general pulmonologists not meeting ATS or CHEST minimum requirements practice at the same institution. Proponents of a more liberal access to credentialing in EBUS have suggested that adhering to competency requirements constitutes a "barrier to entry" in which incumbent practitioners benefit from limiting competition. However, like any other regulatory metric, the rationale is to prevent asymmetric information. In this example, the physician knows more than the patient. The patient cannot make an informed decision on which provider to choose and what are the minimum requirements that are likely to produce the most useful information (ie, complete staging). For these reasons, it is imperative



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that regulations protect the patient. Without question, EBUS bron-

choscopy should not be performed only by board-certified interventional pulmonologists. Instead, hospital credentialing committees should adhere to both the ATS and CHEST recommendations for the number of supervised cases necessary prior to

### Proponents of a more liberal access to credentialing in EBUS have suggested that adhering to competency requirements constitutes a "barrier to entry" in which incumbent practitioners benefit from limiting competition.

performing EBUS independently. As EBUS use continues to grow, fellows in 3- or 4-year pulmonary and critical

care fellowships will be likely capable of meeting the minimal number of observed cases, but, if these numbers

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are not achieved, additional training should be required. Understandably, this could be challenging for physicians who are unable to take time away from their practice to gain this training. However, if these numbers cannot be met, credentialing requirements should be enforced.

Even more challenging than establishing quality measures for EBUS, is to ensure the highest level of care delivery for patients when there exist multiple levels of experience in the same institution. Undoubtedly, patients undergoing EBUS bronchoscopy, or any procedure for that matter, would want the most skilled physician who has attained certification in the procedure. Unfortunately, no formal certification of EBUS exists outside of gaining board certification in interventional pulmonology. To ensure excellence in care, physicians performing EBUS should be involved in quality improvement initiatives and review pathologic yields along with complications on a regular basis in a group setting. Unlike emergency interventions, EBUS bronchoscopy is an entirely elective procedure.

The advent of EBUS bronchoscopy has revolutionized the diagnosis and staging of lung cancer. As use of EBUS continues to become more widespread, the incidence of high volume and low volume proceduralists will become a more commonly encountered scenario. Guidelines have been set by the professional pulmonary societies based on the data and observations available. At the local level, stringent guidelines need to be established by hospitals to ensure a high level of quality with appropriate oversight. Patients undergoing EBUS deserve a physician who is skilled in the procedure and has performed at least the minimum number of procedures to provide the adequate care.

Dr. Mahajan is Medical Director, Interventional Pulmonology, Inova Heart and Vascular Institute - Inova Fairfax Hospital, and Associate Professor, Virginia Commonwealth Medical School; Dr. Khandhar is Medical Director, Thoracic Surgery, Inova Heart and Vascular Institute - Inova Fairfax Hospital, and Assistant Clinical Professor, Virginia Commonwealth Medical School; Falls Church, VA. Dr. Folch is Co-Director, Interventional Pulmonology Chief, Complex Chest Diseases Center, Harvard Medical School, Massachusetts General Hospital, Boston, MA.

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### **EDITOR'S NOTE**

r. Mahajan and colleagues present a compelling case for requiring minimum standards to perform an EBUS-guided bronchoscopy. Their opinion piece epitomizes the classic tension between physicians with advanced training and those who can only have practice-based training. A middle ground may exist, as perhaps competence could be achieved by simulation, clinical cases performed, and observation by a regional expert? Physicians in practice must have a pathway to adopt new technology whether it is thoracic ultrasound or endobronchial ultrasound, but it must be done in a safe manner. As a referring physician, I would only send my patients who required mediastinal staging to a pulmonologist who I knew performed EBUS regularly.

Nitin Puri, MD, FCCP

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

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Clinical Predictors of Hospital Mortality Differ Between Direct and Indirect ARDS. By Dr. L. Luo, et al.

Cross-Disciplinary Analysis of Lymph Node Classification in Lung Cancer on CT Scanning. By Dr. A. H. El-Sherief, et al. (Podcast)

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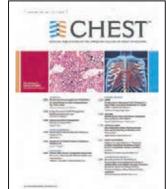
Professor James C. Hogg. By Dr. Manuel G. Cosio.

#### COMMENTARY

Pulmonary Hypertension Care Center Network: Improving Care and Outcomes in Pulmonary Hypertension. By Dr. S. Sahay, et al.

### EVIDENCE-BASED MEDICINE

Use of Management Pathways or Algorithms in Children With Chronic Cough: CHEST Guideline and Expert Panel Report. By Dr. A. B.



Chang, et al; on behalf of the CHEST Expert Cough Panel.

Symptomatic Treatment of Cough Among Adult Patients With Lung Cancer: CHEST Guideline and Expert Panel Report. By Dr. A. Molassiotis, et al; on behalf of the CHEST Expert Cough Panel.

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### NETWORKS: Uranium mining, hyperoxia, palliative care education, OSA impact

### **Occupational and Environmental Health**

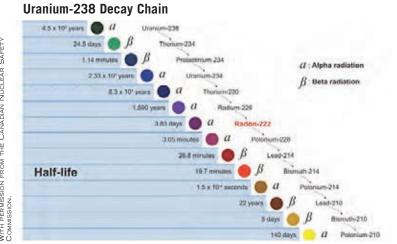
### Health effects of uranium mining Decay series of U 238

Prior to 1900, uranium was used only for coloring glass. After discovery of radium by Madame Curie in 1898, uranium was widely mined to obtain radium (a decay product of uranium).

While uranium was not directly mined until 1900, uranium contaminates were in the ore in silver and cobalt mines in Czechoslovakia, which were heavily mined in the 18th and 19th centuries.

Increased mortality was described in these miners in 1770. In 1878, Harting and Hesse (a public health officer and a local mine physician) described 23% mortality from lung cancer in 650 Schneeberg cobalt miners over 10 years. By the 1920s, 50% of exposed miners were dying of lung cancer.

There were no reports (written in English) of lung cancer associated with



radiation until 1942; but in 1944, these results were called into question in a monograph from the National Cancer Institute. The carcinogenicity of radon was confirmed in 1951; however, this remained an internal government document until 1980. By 1967, the increased prevalence of lung cancer in uranium miners was widely known. By 1970, new ventilation standards for uranium mines were established.

Lung cancer risk associated with uranium mining is the result of exposure to radon gas and specifically radon progeny of Polonium 218 and 210. These radon progeny remain suspended in air, attached to ambient particles (diesel exhaust, silica) and are then inhaled into the lung, where they tend to precipitate on the major airways. Polonium 218 and 210 are alpha emitters, which have a 20-fold increase in energy compared with gamma rays (the primary radiation source in radiation therapy). Given the mass of alpha particles (two protons and two neutrons), they interact with superficial tissues; thus, once deposited in the large airways, a large radiation dose is directed to the respiratory epithelium of these airways.

Occupational control of exposure to radon and radon progeny is accomplished primarily by ventilation. In high-grade deposits of uranium, such as the 20% ore grades in the Athabasca Basin of Saskatchewan, remote control mining is performed.

Smoking, in combination with occupational exposure to radon progeny, carries a greater than additive but less than multiplicative risk of lung cancer.

In addition to the lung cancer risk associated with radon progeny exposure, uranium miners share the occupational risks of other miners: exposure to silica and diesel exhaust. Miners are also at risk for traumatic injuries, including electrocution.

Health effects associated with uranium milling, enrichment, and tailings will be discussed in a subsequent CHEST Physician article.

Richard B. Evans, MD, MPH, FCCP Steering Committee Chair

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**Comprehensive Bronchoscopy With Endobronchial Ultrasound** September 29-October 1 CME credits and MOC points: 21.00 Key topics: Biopsy, brushings, conventional and EBUS-guided

TBNA, radial EBUS for peripheral nodules, management of airway bleeding and aspirated foreign objects, and lung cancer diagnosis and staging strategies





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### **Respiratory Care**

Hyperoxia in critically ill

patients: What's the verdict?

Oxygen saturation is considered to be the "fifth vital sign," and current guidelines recommend target oxygen saturation (SpO<sub>2</sub>) between 94% and 98%, with lower targets for patients at risk for hypercapnic respiratory failure (O'Driscoll BR et al. *Thorax.* 2008;63(suppl):vi1). Oxygen toxicity is well-demonstrated in



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Round 1 winners will be determined by the top two NetWork Steering Committees with the highest percentage of participation.

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- on Monday from 1:30 pm to 2:30 pm.



### ROUND 2 July- CHEST 2017

Who: NetWork Steering Committee members

How to Participate: Members will compete by donating or pledging any amount to the CHEST Foundation in 2017.

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Proceeds donated in Round 2 will fund two new community service initiatives, which will be chosen and created by the two winning NetWorks.

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Round 2 winners will be determined by the total amount contributed by the top two NetWorks Steering Committees.

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- Up to two travel grants to CHEST 2018.

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#### ROUND 3 CHEST 2017

Who: All CHEST NetWork Members

How to Participate: Members will compete by donating

Members will compete by donating or pledging any amount to the CHEST Foundation during CHEST 2017.

#### Where Your Money Goes:

Proceeds donated in Round 3 will fund two new patient education guides. The topics of the guides will be chosen and created by the two winning NetWorks.

#### How to Win:

Round 3 winners will be determined by the highest percentage of participation by the top two NetWorks' membership.

#### What You Win:

The two winning NetWork Steering Committees receive the following:

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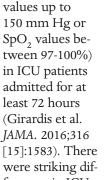
experimental animal studies. While its incidence and impact on outcomes is difficult to determine in the clinical setting, increases in-hospital mortality have been associated with hyperoxia in patients with cardiac arrest, acute myocardial infarction, and stroke (Kligannon et al. *JAMA*. 2010;303[21]:2165; Stub et al. *Circulation*. 2015;131[24]:2143; Rincon et al. *Crit Care Med*. 2014;42[2]:387).

Girardis and colleagues examined

the impact of conservative oxygen administration (PaO<sub>2</sub> maintained between 70-100 mm Hg or SpO<sub>2</sub> between 94-98%) vs standard care group (permitting PaO<sub>2</sub>



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mortality between the two groups with absolute risk reduction of 8.6% (P = .01) favoring the conservative oxygen therapy group, as well as significant reductions in episodes of shock, liver failure, and bacteremia. However, there were baseline differences in the severity of illness between the two groups: the use of a modified intention to treat analysis and the early termination of the trial mitigate the robustness of these findings.

Complementing the findings of Girardis and colleagues, a recent analysis of more than 14,000 critically ill patients, found that time spent at  $PaO_2 > 200 \text{ mm Hg was associated}$  with excess mortality and fewer ventilator-free days (Helmerhorst et al. *Crit Care Med.* 2017;45[2]:187).

While other trials demonstrated safety and feasibility of conservative oxygen therapy in critically ill patients (Panwar et al. Am J Respir Crit Care Med. 2016;193[1]:43; Helmerhorst et al. *Crit Care Med.* 2016; 44[3]:554; Suzuki et al. *Crit Care Med.* 2014;42[6]:1414), they did not find significant differences between conservative and liberal oxygen therapy with regards to new organ dysfunction or mortality. However, the degree of hyperoxia was usually more modest than in either the Girardis trial or the Helmerhorst (2017) analysis.

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least 72 hours (Girardis et al. *JAMA*. 2016;316 [15]:1583). Ther were striking di ferences in ICU

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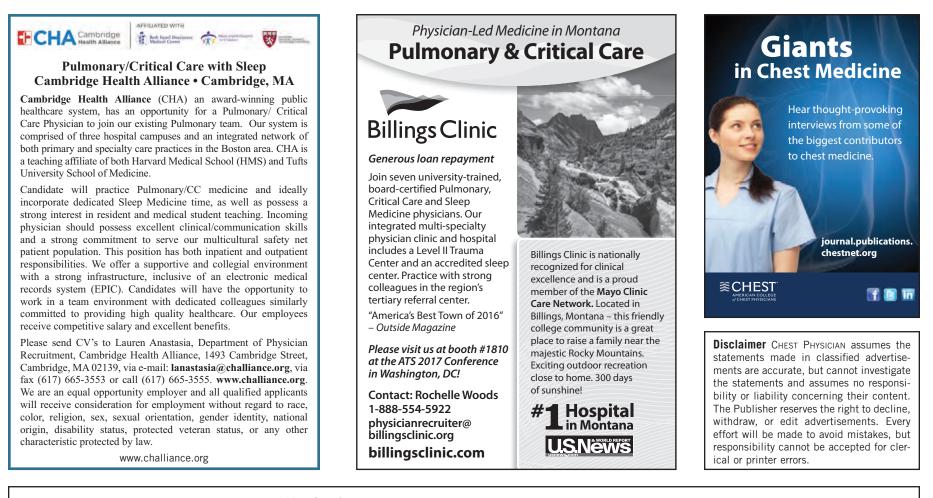
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Based on current evidence, it seems appropriate to maintain physiologically normal levels of PaO<sub>a</sub> without causing hyperoxia in critically ill patients. Oxygen saturation greater than 97% or 98% for prolonged periods should be avoided. Further randomized controlled trials are needed to more clearly elucidate appropriate targets for oxygenation and their impact on patient outcomes.

Amanpreet Kaur, MD Steering Committee Fellow-in-Training David L. Bowton, MD, FCCP Steering Committee Chair

### Palliative and **End-of-Life Care**

Education in palliative medicine Prompted by concerns that the Affordable Care Act would be instituting "death panels" as part of



cost-containment measures, "Dying in America" (a 2015 report of the Institute of Medicine [IOM]) identified compassionate, affordable, and effective care

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for patients at the end of their lives as a "national priority" in American health care. The IOM identified the education of all primary care providers in the delivery of basic palliative care, specifically commenting that all clinicians who manage patients with serious, life-threatening illnesses should be "competent in basic palliative care" (IOM, The National Academies Press 2015).

Considerable effort has been put into providing clinicians with tools to gain this competence. Resources exist from organizations, ranging from the American Academy of Hospice and Palliative Medicine to the American College of Surgeons. Numerous publications address everything from symptom management to teaching communication skills to medical students and residents. But the question remains - can physicians who have been trained to "tread with care in matters of life and death" balance comfort with cure (Lasagna 1964, Modern Hippocratic Oath)? We believe the answer ultimately is yes, and that this balance may prove to be the antidote to the pervasive issues of burnout that plague our profession.

Check out our NetWork Storify page later this year for links to the ongoing discussion surrounding palliative care in medicine and for useful tools in the effort to provide palliative care to all our patients.

> Laura Johnson, MD, FCCP Steering Committee Vice Chair

### **Sleep Medicine**

### The impact of sleep apnea: Why should we care?

With recent large trials such as the SAVE and the SERVE-HF studies challenging the cardiovascular ben-



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field to CHEST 2017 to discuss their take on where we stand with the connection between sleep-disordered breathing and cardiovascular disease, so stay tuned!

leaders in the

Meanwhile, we might reflect on the safety, social, and economic impacts of OSA and its treatment. Sleepiness due to OSA significantly affects driving performance and has received significant attention from the Federal Motor Carrier Safety Administration (FMCSA). Patients with OSA are six times more likely to have a motor vehicle crash than those without OSA (Terán-Santos et al. N Engl J Med. 1999;340[11]:847). One transportation company, Schneider, has incorporated an OSA screening and treatment program and reported a 73% reduction in preventable driving accidents.

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Our relationships, general health, and work productivity can be affected by untreated OSA. The effect on daily life may not be initially obvious. Patients often present only at the insistence of their partner or physician, only to be surprised at how much better they feel once treated. Symptoms of OSA are associated with a higher rate of impaired work performance, sick leave, and divorce (Grunstein et al. Sleep. 1995;18[8]:635). A recent survey estimates an \$86.9 billion loss of workplace productivity due to sleep apnea in 2015 (Frost & Sullivan. Hidden health crisis costing America billions. AASM; 2016. http://www.aasmnet.org/Resources/pdf/sleep-apnea-economic-crisis. pdf. Accessed March 21, 2017.). The same survey found that among those who are employed, treating OSA was associated with a decline in absences by 1.8 days per year and an increase in productivity 17.3% on average. Considering that the majority of OSA remains undiagnosed, this could have tremendous economic impact.

OSA is an important public health burden. The Sleep NetWork is committed to increasing awareness among individuals (patients and clinicians) and institutions (transportation agencies, government) of the impact of sleep-disordered breathing on society. Aneesa Das, MD, FCCP Steering Committee Chair

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#### Food

Are you a foodie? Or do you just enjoy a great meal? Breakfast and brunch are the best ways to start off your day, and there's no shortage of spots in the Toronto area to get your fix. No matter what you're craving, there's a place for you.

Le Petit Dejeune offers an ever-changing menu that ranges from less expensive items, like soup, sandwiches, and salads, to some pricier stuffed crepes, quiche, and eggs florentine. While most Sundays, Saving Grace is packed, but there's only a 15-minute wait, and the atmosphere is quite pleasant. Looking for the perfect cinnamon bun? Rosen's Cinnamon Buns is the place to go. But you have to look closely for the bakery's name, since the sign above the window still advertises the hair salon that used to reside in the same spot!

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### **Nature parks**

One of the city's largest and oldest parks, High Park is Toronto's version of New York City's Central Park. There's plenty to enjoy, such as Grenadier Pond, numerous ravine-based hiking trails, playgrounds, athletic areas, restaurants, a museum, and even a zoo!

If you want a different type of nature excursion, there is always beautiful Niagara Falls, Ontario, which is just a short drive from Toronto. Don't miss seeing the Tesla monument in Queen Victoria Park, or go 10 minutes north of the Falls to the Botanical Gardens, home to the Butterfly Conservatory with over 2,000 butterflies.

#### Relaxation

After eventful days of absorbing all the new science CHEST 2017 has to offer, you may want to relax your mind and body. Elmwood spa, located

in downtown Toronto, is where "four spacious floors of treatment and renewal options mean that Elmwood Spa can provide the convenience and flexibility to cater to demanding schedules," according to Elmwood.

Learn more about Toronto opportunities at blogTO.com, and find out more about CHEST 2017 at chestmeeting.chestnet.org.

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# **E K**)**O**)**S**)<sup>°</sup>

### Dear Clot, You really don't take my breath away.

The EKOS<sup>®</sup> System quickly improves right ventricular function and pulmonary <u>artery pressure.<sup>1</sup></u>

EKOS<sup>®</sup> does much more than the current standard of PE care. It speeds time to dissolution by unwinding the clot's fibrin structure, allowing greater lytic dispersion and accelerated absorption.<sup>2</sup> It also minimizes bleeding risk, requiring up to 4x less drug dosage than systemic delivery.<sup>3.4</sup>

Visit **www.ekoscorp.com** to learn more about the only endovascular device cleared by the FDA for the treatment of pulmonary embolism.

- <sup>1</sup> In the Seattle II study of 150 patients with massive or submassive PE using an EKOS® and lytic combination, the mean RV/LV ratio decreased from 1.55 preprocedure to 1.13 at 48 hours post-procedure (P<0.0001) while PA systolic pressure decreased from 51.4mmHg to 36.9mmHg (P<0.0001).
- <sup>2</sup> Braaten, J et al., Thromb Haemost 1997;78:1063-8; Francis, C et al. Ultrasound in Medicine and Biology 1995; 21(3):419-424; Soltani, A et al., Physics in Medicine and Biology 2008; 53:6837-6847
- <sup>3</sup> Kucher, N., et al., Circulation, Vol. 129, No. 4, 2014, 479–486.
- <sup>4</sup> Piazza, G., et al., American College of Cardiology 63rd Annual Scientific Session, Wash D.C., March 30, 2014.

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



### EKOS CORPORATION | 11911 N. Creek Pkwy S. | Bothell, WA 98011 | 888.400.3567 | EKOSCORP.COM

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