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COURTESY DR. APARNA SWAMINATHAN

"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

Children with poor lung function will be more likely to develop asthma-chronic 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_1 [forced expiratory volume in 1 second] and FEV_1/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

A 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 norepinephrine 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*

Pulmonary embolism common in patients with AE-COPD

BY JIM KLING
Frontline Medical News

FROM CHEST

About 16% of patients with 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*

INSIDE

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- **Esbriet delayed progression of IPF vs placebo through a sustained impact on lung function decline in ASCEND[2,3]**
- **No statistically significant difference vs placebo in change in %FVC or decline in FVC volume from baseline to 72 weeks was observed in CAPACITY 006[2,4]**
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ATS=American Thoracic Society; ERS=European Respiratory Society; JRS=Japanese Respiratory Society; ALAT=Latin American Thoracic Association; %FVC=percent predicted forced vital capacity.

*The efficacy of Esbriet was evaluated in three phase 3, randomized, double-blind, placebo-controlled, multicenter trials. In ASCEND, 555 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo for 52 weeks. Eligible patients had %FVC between 50%-90% and $\%DL_{co}$ (percent predicted diffusing capacity of lung for carbon monoxide) between 30%-90%. The primary endpoint was change in %FVC from baseline to week 52. In CAPACITY 006, 344 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo. Eligible patients had %FVC ≥50% and $\%DL_{co}$ ≥35%. The primary endpoint was change in %FVC from baseline to week 72.

†Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences.

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Photosensitivity reaction or rash: Patients treated with Esbriet had a higher incidence of photosensitivity reactions (9%) compared with patients treated with placebo (1%). Patients should avoid or minimize exposure to sunlight (including sunlamps), use a sunblock (SPF 50 or higher), and wear clothing that protects against sun exposure. Patients should avoid concomitant medications that cause photosensitivity. Dosage reduction or discontinuation may be necessary.

Gastrointestinal disorders: Gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastroesophageal reflux disease, and abdominal pain were more frequently reported in patients treated with Esbriet. Dosage reduction or interruption for gastrointestinal events was required in 18.5% of patients in the Esbriet 2403 mg/day group, as compared to 5.8% of patients in the placebo group; 2.2% of patients in the Esbriet 2403 mg/day group discontinued treatment due to a gastrointestinal event, as compared to 1.0% in the placebo group. The most common (>2%) gastrointestinal events that led to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. Dosage modifications may be necessary in some cases.

Adverse reactions: The most common adverse reactions (≥10%) were nausea, rash, abdominal pain, upper respiratory tract infection, diarrhea, fatigue, headache, dyspepsia, dizziness, vomiting, anorexia, gastroesophageal reflux disease, sinusitis, insomnia, weight decreased, and arthralgia.

Drug interactions: Concomitant administration with strong inhibitors of CYP1A2 (eg, fluvoxamine) significantly increases systemic exposure of Esbriet and is not recommended. Discontinue prior to administration of Esbriet. If strong CYP1A2 inhibitors cannot be avoided, dosage reductions of Esbriet are recommended. Monitor for adverse reactions and consider discontinuation of Esbriet as needed.

Concomitant administration of Esbriet and ciprofloxacin (a moderate inhibitor of CYP1A2) moderately increases exposure to Esbriet. If ciprofloxacin at the dosage of 750 mg twice daily cannot be avoided, dosage reductions are recommended. Monitor patients closely when ciprofloxacin is used.

Agents that are moderate or strong inhibitors of both CYP1A2 and CYP isoenzymes involved in the metabolism of Esbriet should be avoided during treatment.

The concomitant use of a CYP1A2 inducer may decrease the exposure of Esbriet, and may lead to loss of efficacy. Concomitant use of strong CYP1A2 inducers should be avoided.

Specific populations: Esbriet should be used with caution in patients with mild to moderate (Child-Pugh Class A and B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed. The safety, efficacy, and pharmacokinetics of Esbriet have not been studied in patients with severe hepatic impairment. Esbriet is not recommended for use in patients with severe (Child-Pugh Class C) hepatic impairment.

Esbriet should be used with caution in patients with mild (CL_{cr} 50-80 mL/min), moderate (CL_{cr} 30-50 mL/min), or severe (CL_{cr} less than 30 mL/min) renal impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed. The safety, efficacy, and pharmacokinetics of Esbriet have not been studied in patients with end-stage renal disease requiring dialysis. Use of Esbriet in patients with end-stage renal disease requiring dialysis is not recommended.

Smoking causes decreased exposure to Esbriet, which may alter the efficacy profile of Esbriet. Instruct patients to stop smoking prior to treatment with Esbriet and to avoid smoking when using Esbriet.

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References: 1. Data on file. Genentech, Inc. 2015. **2.** Esbriet Prescribing Information. Genentech, Inc. September 2015. **3.** King TE Jr, Bradford WZ, Castro-Bernardini S, et al; for the ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis [published correction appears in *N Engl J Med.* 2014;371(12):1172]. *N Engl J Med.* 2014;370(22):2083-2092. **4.** Noble PW, Albera C, Bradford WZ, et al; for the CAPACITY Study Group. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet.* 2011;377(9779):1760-1769. **5.** Raghu G, Rochwerg B, Zhang Y, et al; ATS, ERS, JRS, and ALAT. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical practice guideline [published correction appears in *Am J Respir Crit Care Med.* 2015;192(5):644]. *Am J Respir Crit Care Med.* 2015;192(2):e3-e19.

Esbriet®
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Low FEV_1 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_1/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-

istics, such as their percent predicted FEV_1 and percent predicted FEV_1/FVC at 7 years, the investigators said.

Patients in the lowest quartile for FEV_1 percent predicted at 7 years were 2.93 times more likely to have ACOS, compared with patients in the other quartiles for FEV_1 percent predicted. Patients in the lowest quartile for FEV_1/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_1 and FEV_1/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 analysis showed that patients in the lowest quartile for FEV_1 had an odds ratio of 2.4 for ACOS and that those patients in the lowest quartile for FEV_1/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_1 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_1/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_1/FVC were 19.1 times more likely to have ACOS, and patients in the second quartile for FEV_1/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_1 (percent predicted values) over time. Those with COPD alone or ACOS had significantly lower pre-BD FEV_1/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

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," 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 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 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."

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

DR. GARTMAN

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 long-term 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

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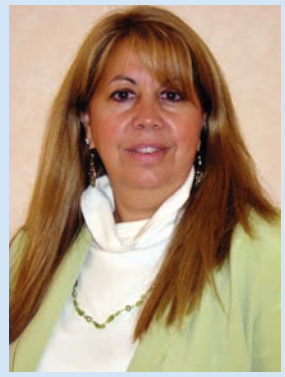

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STEMI team repurposed for rapid treatment of PEs

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.

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.

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, Dr. Kendall noted.

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 already 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 pulmonary 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.

klennon@frontlinemedcom.com

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 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.

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!

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.

Patients with PE were less likely to have symptoms consistent with a respiratory tract infection. They also tended to have higher mortality rates and longer hospitalization rates compared with those without PE.

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.

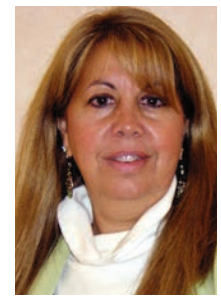
The meta-analysis had some limitations, including the heterogeneity of findings in the included studies, as well as the potential for publication bias, since reports showing unusually low or high rates may be more likely to be published, the researchers noted. There was also a high proportion of male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

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.



BREO® ELLIPTA®
(fluticasone furoate 100 mcg and vilanterol 25 mcg inhalation powder)

For appropriate adult patients

CONSIDER MAKING **24-HOUR BREO** YOUR GO-TO ICS/LABA OPTION

BREO 100/25 is for maintenance treatment of airflow obstruction in patients with COPD, and for reducing COPD exacerbations in patients with a history of exacerbations. BREO 100/25 is the only strength indicated for COPD.

BREO is for adult patients with asthma uncontrolled on an ICS or whose disease severity clearly warrants an ICS/LABA.

BREO is NOT indicated for the relief of acute bronchospasm.

Important Safety Information

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths. This finding with salmeterol is considered a class effect of all LABA. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids (ICS) or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients.

BOXED WARNING CONTINUED ON NEXT PAGE

Please see additional Important Safety Information for BREO on pages 2–4.
Please see accompanying Brief Summary of Prescribing Information, including Boxed Warning, for BREO on pages 5–7.

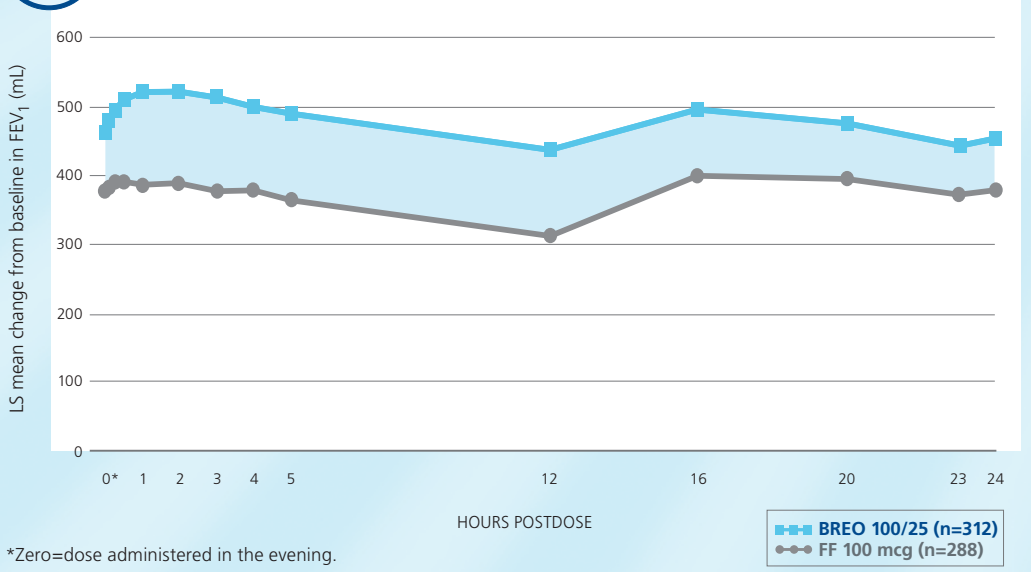
BREO:
CONTINUOUS LUNG FUNCTION IMPROVEMENT

In patients with **asthma** uncontrolled on an ICS

BREO 100/25 (n=312) provided a 108-mL improvement from baseline in weighted mean (wm) FEV_1 (0-24 hours) vs fluticasone furoate (FF) 100 mcg (n=288) at Week 12 (*P*<0.001).[1]

BREO 100/25

SERIAL FEV_1 (0-24 HOURS) AT WEEK 12[1]



*Zero=dose administered in the evening.

Study description

Design: 12-week, randomized, double-blind study that evaluated the safety and efficacy of BREO 100/25, BREO 200/25, and FF 100 mcg (each administered once daily in the evening). Patients who reported symptoms and/or rescue $beta_2$-agonist use during a 4-week run-in period on mid- to high-dose ICS (≥250 mcg fluticasone propionate [FP] twice daily or equivalent) were randomized to treatment.

Patients: 1039 patients with asthma aged 12 years and older[††] (mean age: 46 years). At baseline, patients had a mean percent predicted FEV_1 of 62%.

[††] BREO is approved for use in patients ≥18 years of age.

Primary endpoint: wm FEV_1 (0-24 hours) at Week 12.

Weighted mean FEV_1 (0-24 hours) was calculated from predose FEV_1 (within 30 minutes of dose) and postdose FEV_1 after 5, 15, and 30 minutes and 1, 2, 3, 4, 5, 12, 16, 20, 23, and 24 hours.

FEV_1=forced expiratory volume in 1 second; LS=least squares.

In a placebo-controlled 12-week study[2]:

- **wm FEV_1:** in a subset of patients, BREO 100/25 (n=108) demonstrated a numerically greater improvement in change from baseline in wm FEV_1 (0-24 hours) compared with FF 100 mcg (n=106) of 116 mL (95% CI: –5, 236; *P*=0.06) and a statistically significant 302-mL improvement (*P*<0.001) compared with placebo (n=95) at Week 12.

Study description: 12-week, randomized, double-blind, placebo-controlled study of 609 patients aged 12 years and older[†] (mean age: 40 years) with asthma, symptomatic on low- to mid-dose ICS (FP 100 mcg to 250 mcg twice daily or equivalent) during a 4-week run-in period (mean baseline percent predicted FEV_1 of 70%) randomized to BREO 100/25, FF 100 mcg, or placebo (each administered once daily in the evening). The co-primary endpoints were weighted mean FEV_1 (0-24 hours) (in a subset of patients) and trough FEV_1 at Week 12.

[†] BREO is approved for use in patients ≥18 years of age.

Important Safety Information (cont'd)

WARNING: ASTHMA-RELATED DEATH
(BOXED WARNING cont'd)

When treating patients with asthma, only prescribe BREO for patients not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue BREO) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS. Do not use BREO for patients whose asthma is adequately controlled on low- or medium-dose ICS.

CONTRAINDICATIONS

The use of BREO is contraindicated in the following conditions:

- Primary treatment of status asthmaticus or other acute episodes of COPD or asthma where intensive measures are required.
- Severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone furoate, vilanterol, or any of the excipients.

WARNINGS AND PRECAUTIONS

- BREO should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD or asthma.
- BREO should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled, short-acting $beta_2$-agonist.
- BREO should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using BREO should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

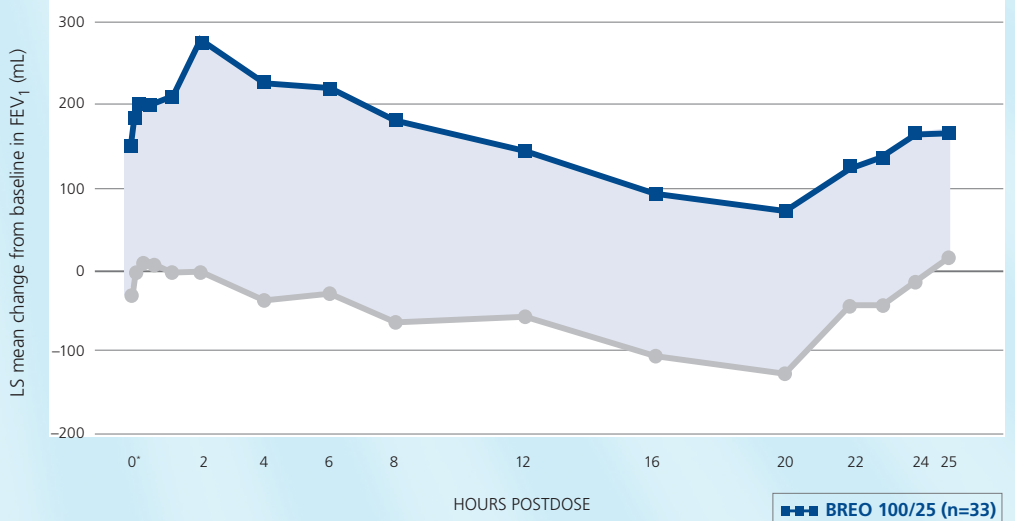
FOR A FULL 24 HOURS, WITH JUST ONE DAILY INHALATION

In patients with COPD

BREO 100/25 (n=33) provided a 220-mL improvement from baseline in wm FEV_1 (0-24 hours) vs placebo (n=51) at end of the 28-day treatment period (*P*<0.001).[3,4]

BREO 100/25

SERIAL FEV_1 (0-25 HOURS) ASSESSED OVER 1 FULL DAY AT DAYS 28 AND 29[3,4]



*Zero=dose administered in the morning.

Study description

Design: randomized, double-blind, crossover study compared the effect of 28 days of treatment with BREO 100/25 and placebo (each administered once daily in the morning) on lung function over 24 hours.

Patients: 54 patients (mean age: 58 years) with COPD who had a mean percent predicted postbronchodilator FEV_1 of 50% and a mean postbronchodilator FEV_1/FVC ratio of 53%.

Primary endpoint: wm FEV_1 (0-24 hours) at end of 28-day treatment period.

Secondary endpoint: serial FEV_1 (0-25 hours) assessed over 1 full day at Days 28 and 29.

FVC=forced vital capacity.

BREO 100/25 is the only strength indicated for COPD.

In a separate 6-month lung-function study: a randomized, double-blind, parallel-group study compared the effect of BREO 100/25 vs FF 100 mcg and vs placebo (each administered once daily) on lung function in 1030 patients (mean age: 63 years) with COPD.[§] For the co-primary endpoints, BREO significantly improved wm FEV_1 (0-4 hours) postdose on Day 168 by 120 mL vs FF[‖] and 173 mL vs placebo (*P*<0.001 for both); and BREO demonstrated a greater difference in LS mean change from baseline in trough FEV_1 at Day 169 of 115 mL vs placebo (95% CI: 60, 169; *P*<0.001); the 48-mL difference vs vilanterol (VI) 25 mcg[¶] did not achieve statistical significance (95% CI: –6, 102; *P*=0.082).[3,5]

[§]At screening, patients had a mean postbronchodilator percent predicted FEV_1 of 48% and a mean postbronchodilator FEV_1/FVC ratio of 48%.
[‖]The wm comparison of BREO with FF, the ICS component, evaluated the contribution of VI to BREO. ICS are not approved as monotherapy for COPD.
[¶]The trough FEV_1 comparison of BREO with VI, the LABA component, evaluated the contribution of FF to BREO. VI is not approved as monotherapy.

Important Safety Information (cont'd)
WARNINGS AND PRECAUTIONS (cont'd)

- Oropharyngeal candidiasis has occurred in patients treated with BREO. Advise patients to rinse the mouth with water without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.
- An increase in the incidence of pneumonia has been observed in subjects with COPD receiving BREO. There was also an increased incidence of pneumonias resulting in hospitalization. In some incidences these pneumonia events were fatal.
  - In replicate 12-month studies of 3255 subjects with COPD who had experienced a COPD exacerbation in the previous year, there was a higher incidence of pneumonia reported in subjects receiving BREO 100/25 (6% [51 of 806 subjects]), fluticasone furoate (FF)/vilanterol (VI) 50/25 mcg (6% [48 of 820 subjects]), and BREO 200/25 (7% [55 of 811 subjects]) than in subjects receiving VI 25 mcg (3% [27 of 818 subjects]). There was no fatal pneumonia in subjects receiving VI or FF/VI 50/25 mcg. There was fatal pneumonia in 1 subject receiving BREO 100/25 and in 7 subjects receiving BREO 200/25 (<1% for each treatment group).

References: 1. Bernstein DI, Bateman ED, Woodcock A, et al. Fluticasone furoate (FF)/vilanterol (100/25 mcg or 200/25 mcg) or FF (100 mcg) in persistent asthma. *J Asthma*. 2015;52(10):1073-1083. **2.** Bleecker ER, Lötvall J, O'Byrne PM, et al. Fluticasone furoate-vilanterol 100-25 mcg compared with fluticasone furoate 100 mcg in asthma: a randomized trial. *J Allergy Clin Immunol Pract*. 2014;2(5):553-561. **3.** Data on file, GSK. **4.** Boscia JA, Pudi KK, Zvarich MT, Sanford L, Siederer SK, Crim C. Effect of once-daily fluticasone furoate/vilanterol on 24-hour pulmonary function in patients with chronic obstructive pulmonary disease: a randomized, three-way, incomplete block, crossover study. *Clin Ther*. 2012;34(8):1655-1666. **5.** Kerwin EM, Scott-Wilson C, Sanford L, et al. A randomised trial of fluticasone furoate/vilanterol (50/25 µg; 100/25 µg) on lung function in COPD. *Respir Med*. 2013;107(4):560-569.

Please see additional Important Safety Information for BREO on pages 1, 2, and 4.

Please see accompanying Brief Summary of Prescribing Information, including Boxed Warning, for BREO on pages 5–7.

BREO® ELLIPTA®
(fluticasone furoate 100 mcg and vilanterol 25 mcg inhalation powder)

CONSIDER **24-HOUR BREO** TODAY

Important Safety Information (cont'd)
WARNINGS AND PRECAUTIONS (cont'd)

- Physicians should remain vigilant for the possible development of pneumonia in patients with COPD, as the clinical features of such infections overlap with the symptoms of COPD exacerbations.
- Patients who use corticosteroids are at risk for potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. A more serious or even fatal course of chickenpox or measles may occur in susceptible patients. Use caution in patients with the above because of the potential for worsening of these infections.
- Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. Taper patients slowly from systemic corticosteroids if transferring to BREO.
- Hypercorticism and adrenal suppression may occur with very high dosages or at the regular dosage of inhaled corticosteroids in susceptible individuals. If such changes occur, discontinue BREO slowly.
- Caution should be exercised when considering the coadministration of BREO with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue BREO and institute alternative therapy.
- Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of BREO. Discontinue BREO if such reactions occur.
- Vilanterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, BREO may need to be discontinued. BREO should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
- Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating BREO and periodically thereafter.
- Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD or asthma following the long-term administration of inhaled corticosteroids. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Be alert to hypokalemia and hyperglycemia.
- Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to children and adolescents.

ADVERSE REACTIONS: BREO 100/25 FOR COPD

- The most common adverse reactions (≥3% and more common than placebo) reported in two 6-month clinical trials with BREO (and placebo) were nasopharyngitis, 9% (8%); upper respiratory tract infection, 7% (3%); headache, 7% (5%); and oral candidiasis, 5% (2%).
- In addition to the events reported in the 6-month studies, adverse reactions occurring in ≥3% of the subjects with COPD treated with BREO in two 1-year studies included back pain, pneumonia, bronchitis, sinusitis, cough, oropharyngeal pain, arthralgia, influenza, pharyngitis, and pyrexia.

ADVERSE REACTIONS: BREO FOR ASTHMA

- In a 12-week trial, adverse reactions (≥2% incidence and more common than placebo) reported in subjects taking BREO 100/25 (and placebo) were: nasopharyngitis, 10% (7%); headache, 5% (4%); oropharyngeal pain, 2% (1%); oral candidiasis, 2% (0%); and dysphonia, 2% (0%). In a separate 12-week trial, adverse reactions (≥2% incidence) reported in subjects taking BREO 200/25 (or BREO 100/25) were: headache, 8% (8%); nasopharyngitis, 7% (6%); influenza, 3% (3%); upper respiratory tract infection, 2% (2%); oropharyngeal pain, 2% (2%); sinusitis, 2% (1%); bronchitis, 2% (<1%); and cough, 1% (2%).
- In addition to the adverse reactions reported in the two 12-week trials, adverse reactions (≥2% incidence) reported in subjects taking BREO 200/25 once daily in a 24-week trial included viral respiratory tract infection, pharyngitis, pyrexia, and arthralgia, and with BREO 100/25 or 200/25 in a 12-month trial included pyrexia, back pain, extrasystoles, upper abdominal pain, respiratory tract infection, allergic rhinitis, pharyngitis, rhinitis, arthralgia, supraventricular extrasystoles, ventricular extrasystoles, acute sinusitis, and pneumonia.
- In a 24- to 76-week trial of subjects with a history of 1 or more asthma exacerbations within the previous 12 months, asthma-related hospitalizations occurred in 1% of subjects treated with BREO 100/25. There were no asthma-related deaths or asthma-related intubations observed in this trial.

DRUG INTERACTIONS

- Caution should be exercised when considering the coadministration of BREO with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and cardiovascular adverse effects may occur.
- BREO should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval, or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists, such as vilanterol, on the cardiovascular system may be potentiated by these agents.
- Use beta-blockers with caution as they not only block the pulmonary effect of beta-agonists, such as vilanterol, but may also produce severe bronchospasm in patients with COPD or asthma.
- Use with caution in patients taking non–potassium-sparing diuretics, as electrocardiographic changes and/or hypokalemia associated with non–potassium-sparing diuretics may worsen with concomitant beta-agonists.

USE IN SPECIFIC POPULATIONS

- BREO is not indicated for use in children and adolescents. The safety and efficacy in pediatric patients (aged 17 years and younger) have not been established.
- Use BREO with caution in patients with moderate or severe hepatic impairment. Fluticasone furoate systemic exposure increased by up to 3-fold in subjects with hepatic impairment. Monitor for corticosteroid-related side effects.

Please see additional Important Safety Information for BREO on pages 1–3.

Please see accompanying Brief Summary of Prescribing Information, including Boxed Warning, for BREO on pages 5–7.

BREO ELLIPTA was developed in collaboration with Theravance

www.BREOprof.com

BREO® ELLIPTA®
(fluticasone furoate 100 mcg and
vilanterol 25 mcg inhalation powder)

BRIEF SUMMARY

BREO® ELLIPTA® 100/25 (fluticasone furoate 100 mcg and vilanterol 25 mcg inhalation powder), for oral inhalation

BREO® ELLIPTA® 200/25 (fluticasone furoate 200 mcg and vilanterol 25 mcg inhalation powder), for oral inhalation

The following is a brief summary only; see full prescribing information for complete product information.

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of LABA. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids (ICS) or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients.

Therefore, when treating patients with asthma, physicians should only prescribe BREO for patients not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue BREO) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS. Do not use BREO for patients whose asthma is adequately controlled on low- or medium-dose ICS *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

1.1 Maintenance Treatment of Chronic Obstructive Pulmonary Disease:
BREO 100/25 is a combination inhaled corticosteroid/long-acting beta$_2$-adrenergic agonist (ICS/LABA) indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. BREO 100/25 is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations. BREO 100/25 once daily is the only strength indicated for the treatment of COPD.
Important Limitation of Use: BREO is NOT indicated for the relief of acute bronchospasm.

1.2 Treatment of Asthma:
BREO is a combination ICS/LABA indicated for the once-daily treatment of asthma in patients aged 18 years and older. LABA, such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients *[see Warnings and Precautions (5.1), Adverse Reactions (6.2), Use in Specific Populations (8.4)]*. Therefore, when treating patients with asthma, physicians should only prescribe BREO for patients not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue BREO) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS. Do not use BREO for patients whose asthma is adequately controlled on low- or medium-dose ICS.
Important Limitation of Use: BREO is NOT indicated for the relief of acute bronchospasm.

4 CONTRAINDICATIONS
The use of BREO is contraindicated in the following conditions:
Primary treatment of status asthmaticus or other acute episodes of COPD or asthma where intensive measures are required *[see Warnings and Precautions (5.2)]*; Severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone furoate, vilanterol, or any of the excipients *[see Warnings and Precautions (5.11), Description (11) of full prescribing information]*.

5 WARNINGS AND PRECAUTIONS

5.1 Asthma-Related Death:
LABA, such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of ICS or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, physicians should only prescribe BREO for patients not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue BREO) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS. Do not use BREO for patients whose asthma is adequately controlled on low- or medium-dose ICS.

A 28-week, placebo-controlled, US trial that compared the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs. 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). The increased risk of asthma-related death is considered a class effect of LABA, including vilanterol, one of the active ingredients in BREO. No trial adequate to determine whether the rate of asthma-related death is increased in subjects treated with BREO has been conducted. Data are not available to determine whether the rate of death in patients with COPD is increased by LABA.

5.2 Deterioration of Disease and Acute Episodes:
BREO should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD or asthma. BREO has not been studied in subjects with acutely deteriorating COPD or asthma. The initiation of BREO in this setting is not appropriate.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If BREO 100/25 no longer controls symptoms of bronchoconstriction; the patient's inhaled, short-acting, beta$_2$-agonist becomes less effective; or the patient needs more short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting a reevaluation of the patient and the COPD treatment regimen should be undertaken at once. For COPD, increasing the daily dose of BREO 100/25 is not appropriate in this situation.

Increasing use of inhaled, short-acting beta$_2$-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of BREO with a higher strength, adding additional ICS, or initiating systemic corticosteroids. Patients should not use more than 1 inhalation once daily of BREO.

BREO should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. BREO has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist.

When beginning treatment with BREO, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms. When prescribing BREO, the healthcare provider should also prescribe an inhaled, short-acting beta$_2$-agonist and instruct the patient on how it should be used.

5.3 Excessive Use of BREO and Use with Other Long-Acting Beta$_2$-Agonists:
BREO should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using BREO should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

5.4 Local Effects of ICS:
In clinical trials, the development of localized infections of the mouth and pharynx with *Candida albicans* has occurred in subjects treated with BREO. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while treatment with BREO continues, but at times therapy with BREO may need to be interrupted. Advise the patient to rinse his/her mouth with water without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.

5.5 Pneumonia:
An increase in the incidence of pneumonia has been observed in subjects with COPD receiving BREO 100/25 in clinical trials. There was also an increased incidence of pneumonias resulting in hospitalization. In some incidences these pneumonia events were fatal. Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations.

In replicate 12-month trials in 3,255 subjects with COPD who had experienced a COPD exacerbation in the previous year, there was a higher incidence of pneumonia reported in subjects receiving fluticasone furoate/vilanterol 50 mcg/25 mcg: 6% (48 of 820 subjects); BREO 100/25: 6% (51 of 806 subjects); or BREO 200/25: 7% (55 of 811 subjects) than in subjects receiving vilanterol 25 mcg: 3% (27 of 818 subjects). There was no fatal pneumonia in subjects receiving vilanterol or fluticasone furoate/vilanterol 50 mcg/25 mcg. There was fatal pneumonia in 1 subject receiving BREO 100/25 and in 7 subjects receiving BREO 200/25 (less than 1% for each treatment group).

5.6 Immunosuppression:
Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If a patient is exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

ICS should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

5.7 Transferring Patients from Systemic Corticosteroid Therapy:
Particular care is needed for patients who have been transferred from systemically active corticosteroids to ICS because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available ICS. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

Patients who have been previously maintained on 20 mg or more of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although BREO may control COPD or asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress, a severe COPD exacerbation, or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress, a severe COPD exacerbation, or a severe asthma attack.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to BREO. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with BREO. Lung function (FEV_1 or peak expiratory flow), beta-agonist use, and COPD or asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension. Transfer of patients from systemic corticosteroid therapy to BREO may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions).

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

5.8 Hypercorticism and Adrenal Suppression:
Inhaled fluticasone furoate is absorbed into the circulation and can be systemically active. Effects of fluticasone furoate on the HPA axis are not observed with the therapeutic doses of BREO. However, exceeding the recommended dosage or coadministration with a strong cytochrome P450 3A4 (CYP3A4) inhibitor may result in HPA dysfunction *[see Warnings and Precautions (5.9), Drug Interactions (7.1)]*.

Because of the possibility of significant systemic absorption of ICS in sensitive patients, patients treated with BREO should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients who are sensitive to these effects. If such effects occur, BREO should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids, and other treatments for management of COPD or asthma symptoms should be considered.

5.9 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors:
Caution should be exercised when considering the coadministration of BREO with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin,

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troleandomycin, voriconazole) because increased systemic corticosteroid and increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full prescribing information]*.

5.10 Paradoxical Bronchospasm:
As with other inhaled medicines, BREO can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with BREO, it should be treated immediately with an inhaled, short-acting bronchodilator; BREO should be discontinued immediately; and alternative therapy should be instituted.

5.11 Hypersensitivity Reactions, Including Anaphylaxis:
Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of BREO. Discontinue BREO if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder medications containing lactose; therefore, patients with severe milk protein allergy should not use BREO *[see Contraindications (4)]*.

5.12 Cardiovascular Effects:
Vilanterol, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, BREO may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

In healthy subjects, large doses of inhaled fluticasone furoate/vilanterol (4 times the recommended dose of vilanterol, representing a 12- or 10-fold higher systemic exposure than seen in subjects with COPD or asthma, respectively) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias. Therefore, BREO, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5.13 Reduction in Bone Mineral Density:
Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing ICS. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating BREO and periodically thereafter. If significant reductions in BMD are seen and BREO is still considered medically important for that patient's COPD therapy, use of medicine to treat or prevent osteoporosis should be strongly considered.

5.14 Glaucoma and Cataracts:
Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD or asthma following the long-term administration of ICS. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

5.15 Coexisting Conditions:
BREO, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.16 Hypokalemia and Hyperglycemia:
Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medications may produce transient hyperglycemia in some patients. In clinical trials evaluating BREO in subjects with COPD or asthma, there was no evidence of a treatment effect on serum glucose or potassium.

5.17 Effect on Growth:
Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to children and adolescents. *[See Use in Specific Populations (8.4) of full prescribing information.]*

6 ADVERSE REACTIONS

LABA, such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of ICS or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. *[See Warnings and Precautions (5.1).]* Systemic and local corticosteroid use may result in the following: *Candida albicans* infection *[see Warnings and Precautions (5.4)]*; Increased risk of pneumonia in COPD *[see Warnings and Precautions (5.5)]*; Immunosuppression *[see Warnings and Precautions (5.6)]*; Hypercorticism and adrenal suppression *[see Warnings and Precautions (5.8)]*; Reduction in bone mineral density *[see Warnings and Precautions (5.13)]*. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience in Chronic Obstructive Pulmonary Disease:
The clinical program for BREO included 7,700 subjects with COPD in two 6-month lung function trials, two 12-month exacerbation trials, and 6 other trials of shorter duration. A total of 2,034 subjects with COPD received at least 1 dose of BREO 100/25, and 1,087 subjects received a higher strength of fluticasone furoate/vilanterol. The safety data described below are based on the confirmatory 6- and 12-month trials. Adverse reactions observed in the other trials were similar to those observed in the confirmatory trials.

6-Month Trials: The incidence of adverse reactions associated with BREO 100/25 is based on 2 placebo-controlled, 6-month clinical trials (Trials 1 and 2; n=1,224 and n=1,030, respectively). Of the 2,254 subjects, 70% were male and 84% were white. They had a mean age of 62 years and an average smoking history of 44 pack-years, with 54% identified as current smokers. At screening, the mean postbronchodilator percent predicted FEV_1 was 48% (range: 14% to 87%), the mean postbronchodilator FEV_1/forced vital capacity (FVC) ratio was 47% (range: 17% to 88%), and the mean percent reversibility was 14% (range: -41% to 152%). Subjects received 1 inhalation once daily of the following: BREO 100/25, BREO 200/25, fluticasone furoate/vilanterol 50 mcg/25 mcg, fluticasone furoate 100 mcg, fluticasone furoate 200 mcg, vilanterol 25 mcg, or placebo.

In Trials 1 and 2, adverse reactions (≥3% incidence and more common than placebo) reported in subjects with COPD taking BREO 100/25 (n=410) (vilanterol 25 mcg [n=408]; fluticasone furoate [n=410]; or placebo [n=412]) were: nasopharyngitis 9% (10%, 8%, 8%); upper respiratory tract infection 7% (5%, 4%, 3%); headache 7% (9%, 7%, 5%); and oropharyngeal candidiasis 5% (2%, 3%, 2%). Oropharyngeal candidiasis includes oral candidiasis, candidiasis, and fungal oropharyngitis.

12-Month Trials: Long-term safety data is based on two 12-month trials (Trials 3 and 4; n=1,633 and n=1,622, respectively). Trials 3 and 4 included 3,255 subjects, of which 57% were male and 85% were white. They had a mean age of 64 years and an average smoking history of 46 pack-years, with 44% identified as current smokers. At screening, the mean postbronchodilator percent predicted FEV_1 was 45% (range: 12% to 91%), and the mean postbronchodilator FEV_1/FVC ratio was 46% (range: 17% to 81%), indicating that the subject population had moderate to very severely impaired airflow obstruction. Subjects received 1 inhalation once daily of the following: BREO 100/25, BREO 200/25, fluticasone furoate/vilanterol 50 mcg/25 mcg, or vilanterol 25 mcg. In addition to the reactions previously mentioned, adverse reactions occurring in greater than or equal to 3% of the subjects treated with BREO 100/25 (n=806) for 12 months included back pain, pneumonia *[see Warnings and Precautions (5.5)]*, bronchitis, sinusitis, cough, oropharyngeal pain, arthralgia, influenza, pharyngitis, and pyrexia.

6.2 Clinical Trials Experience in Asthma:
BREO for the treatment of asthma was studied in 18 double-blind, parallel-group, controlled trials (11 with placebo) of 4 to 76 weeks' duration, which enrolled 9,969 subjects with asthma. BREO 100/25 was studied in 2,369 subjects and BREO 200/25 was studied in 956 subjects. While subjects aged 12 to 17 years were included in these trials, BREO is not approved for use in this age-group *[see Use in Specific Populations (8.4)]*. The safety data described below are based on two 12-week efficacy trials, one 24-week efficacy trial, and two long-term trials.

12-Week Trials: Trial 1 was a 12-week trial that evaluated the efficacy of BREO 100/25 in adolescent and adult subjects with asthma compared with fluticasone furoate 100 mcg and placebo. Of the 609 subjects, 58% were female and 84% were white; the mean age was 40 years.

In Trial 1, adverse reactions (≥2% incidence and more common than placebo) reported in subjects with asthma taking BREO 100/25 (n=201) (fluticasone furoate 100 mcg [n=205] or placebo [n=203]) were: nasopharyngitis, 10% (7%, 7%); headache, 5% (4%, 4%); oropharyngeal pain, 2% (2%, 1%); oral candidiasis, 2% (2%, 0%); and dysphonia, 2% (1%, 0%). Oral candidiasis includes oral candidiasis and oropharyngeal candidiasis.

Trial 2 was a 12-week trial that evaluated the efficacy of BREO 100/25, BREO 200/25, and fluticasone furoate 100 mcg in adolescent and adult subjects with asthma. This trial did not have a placebo arm. Of the 1,039 subjects, 60% were female and 88% were white; the mean age was 46 years.

In Trial 2, adverse reactions (≥2% incidence) reported in subjects with asthma taking BREO 200/25 (n=346) (BREO 100/25 [n=346] or fluticasone furoate 100 mcg [n=347]) were: headache, 8% (8%, 9%); nasopharyngitis, 7% (6%, 7%); influenza, 3% (3%, 1%); upper respiratory tract infection, 2% (2%, 3%); oropharyngeal pain, 2% (2%, 1%); sinusitis, 2% (1%, <1%); bronchitis, 2% (<1%, 2%); and cough, 1% (2%, 1%).

24-Week Trial: Trial 3 was a 24-week trial that evaluated the efficacy of BREO 200/25 once daily, fluticasone furoate 200 mcg once daily, and fluticasone propionate 500 mcg twice daily in adolescent and adult subjects with asthma. Of the 586 subjects, 59% were female and 84% were white; the mean age was 46 years. This trial did not have a placebo arm. In addition to the reactions shown for Trials 1 and 2 above, adverse reactions occurring in greater than or equal to 2% of subjects treated with BREO 200/25 included viral respiratory tract infection, pharyngitis, pyrexia, and arthralgia.

12-Month Trial: Long-term safety data is based on a 12-month trial that evaluated the safety of BREO 100/25 once daily (n=201), BREO 200/25 once daily (n=202), and fluticasone propionate 500 mcg twice daily (n=100) in adolescent and adult subjects with asthma (Trial 4). Overall, 63% were female and 67% were white. The mean age was 39 years; adolescents (aged 12 to 17 years) made up 16% of the population. In addition to the reactions shown for Trials 1 and 2 above, adverse reactions occurring in greater than or equal to 2% of the subjects treated with BREO 100/25 or BREO 200/25 for 12 months included pyrexia, back pain, extrasystoles, upper abdominal pain, respiratory tract infection, allergic rhinitis, pharyngitis, rhinitis, arthralgia, supraventricular extrasystoles, ventricular extrasystoles, acute sinusitis, and pneumonia.

Exacerbation Trial: In a 24- to 76-week trial, subjects received BREO 100/25 (n=1,009) or fluticasone furoate 100 mcg (n=1,010) (Trial 5). Subjects participating in this trial had a history of one or more asthma exacerbations that required treatment with oral/systemic corticosteroids or emergency department visit or in-patient hospitalization for the treatment of asthma in the year prior to trial entry. Overall, 67% were female and 73% were white; the mean age was 42 years (adolescents aged 12 to 17 years made up 14% of the population). While subjects aged 12 to 17 years were included in this trial, BREO is not approved for use in this age-group *[see Use in Specific Populations (8.4)]*. Asthma-related hospitalizations occurred in 10 subjects (1%) treated with BREO 100/25 compared with 7 subjects (0.7%) treated with fluticasone furoate 100 mcg. Among subjects aged 12 to 17 years, asthma-related hospitalizations occurred in 4 subjects (2.6%) treated with BREO 100/25 (n=151) compared with 0 subjects treated with fluticasone furoate 100 mcg (n=130). There were no asthma-related deaths or asthma-related intubations observed in this trial.

6.3 Postmarketing Experience:
In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of BREO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to BREO or a combination of these factors.
Cardiac Disorders: Palpitations, tachycardia.
Immune System Disorders: Hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria.
Musculoskeletal and Connective Tissue Disorders: Muscle spasms.
Nervous System Disorders: Tremor.
Psychiatric Disorders: Nervousness.
Respiratory, Thoracic, and Mediastinal Disorders: Paradoxical bronchospasm.

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4:
Fluticasone furoate and vilanterol, the individual components of BREO, are both substrates of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to fluticasone furoate and vilanterol. Caution should be exercised when considering the coadministration of BREO with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) *[see Warnings and Precautions (5.9), Clinical Pharmacology (12.3) of full prescribing information]*.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants:
Vilanterol, like other beta$_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

7.3 Beta-Adrenergic Receptor Blocking Agents:
Beta-blockers not only block the pulmonary effect of beta-agonists, such as vilanterol, a component of BREO, but may also produce severe bronchospasm in patients with COPD or asthma. Therefore, patients with COPD or asthma should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents

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for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

7.4 Non–Potassium-Sparing Diuretics:
The electrocardiographic changes and/or hypokalemia that may result from the administration of non–potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with non–potassium-sparing diuretics.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy:
Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled trials with BREO in pregnant women. Corticosteroids and $beta_2$-agonists have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Because animal reproduction studies are not always predictive of human response, BREO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women should be advised to contact their physicians if they become pregnant while taking BREO.

Fluticasone Furoate and Vilanterol: There was no evidence of teratogenic interactions between fluticasone furoate and vilanterol in rats at approximately 5 and 40 times, respectively, the maximum recommended human daily inhalation dose (MRHDID) in adults (on a mcg/m^2 basis at maternal inhaled doses of fluticasone furoate and vilanterol, alone or in combination, up to approximately 95 mcg/kg/day).

Fluticasone Furoate: There were no teratogenic effects in rats and rabbits at approximately 4 and 1 times, respectively, the MRHDID in adults (on a mcg/m^2 basis at maternal inhaled doses up to 91 and 8 mcg/kg/day in rats and rabbits, respectively). There were no effects on perinatal and postnatal development in rats at approximately 1 time the MRHDID in adults (on a mcg/m^2 basis at maternal doses up to 27 mcg/kg/day).

Vilanterol: There were no teratogenic effects in rats and rabbits at approximately 13,000 and 160 times, respectively, the MRHDID in adults (on a mcg/m^2 basis at maternal inhaled doses up to 33,700 mcg/kg/day in rats and on an AUC basis at maternal inhaled doses up to 591 mcg/kg/day in rabbits). However, fetal skeletal variations were observed in rabbits at approximately 1,000 times the MRHDID in adults (on an AUC basis at maternal inhaled or subcutaneous doses of 5,740 or 300 mcg/kg/day, respectively). The skeletal variations included decreased or absent ossification in cervical vertebral centrum and metacarpals. There were no effects on perinatal and postnatal development in rats at approximately 3,900 times the MRHDID in adults (on a mcg/m^2 basis at maternal oral doses up to 10,000 mcg/kg/day).

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully monitored.

8.2 Labor and Delivery:
There are no adequate and well-controlled human trials that have investigated the effects of BREO during labor and delivery. Because beta-agonists may potentially interfere with uterine contractility, BREO should be used during labor only if the potential benefit justifies the potential risk.

8.3 Nursing Mothers:
It is not known whether fluticasone furoate or vilanterol are excreted in human breast milk. However, other corticosteroids and $beta_2$-agonists have been detected in human milk. Since there are no data from controlled trials on the use of BREO by nursing mothers, caution should be exercised when it is administered to a nursing woman.

8.4 Pediatric Use:
BREO is not indicated for use in children and adolescents. The safety and efficacy in pediatric patients (aged 17 years and younger) have not been established.

In a 24- to 76-week exacerbation trial, subjects received BREO 100/25 (n=1,009) or fluticasone furoate 100 mcg (n=1,010). Subjects had a mean age of 42 years and a history of one or more asthma exacerbations that required treatment with oral/systemic corticosteroids or emergency department visit or in-patient hospitalization for the treatment of asthma in the year prior to study entry. *[See Clinical Studies (14.2) of full prescribing information.]* Adolescents aged 12 to 17 years made up 14% of the study population (n=281), with a mean exposure of 352 days for subjects in this age-group treated with BREO 100/25 (n=151) and 355 days for subjects in this age-group treated with fluticasone furoate 100 mcg (n=130). In this age-group, 10% of subjects treated with BREO 100/25 reported an asthma exacerbation compared with 7% for subjects treated with fluticasone furoate 100 mcg. Among the adolescents, asthma-related hospitalizations occurred in 4 subjects (2.6%) treated with BREO 100/25 compared with 0 subjects treated with fluticasone furoate 100 mcg. There were no asthma-related deaths or asthma-related intubations observed in the adolescent age-group.

Effects on Growth: Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to children and adolescents. A reduction of growth velocity in children and adolescents may occur as a result of poorly controlled asthma or from use of corticosteroids, including ICS. The effects of long-term treatment of children and adolescents with ICS, including fluticasone furoate, on final adult height are not known. *[See Warnings and Precautions (5.17); Use in Special Populations (8.4) of full prescribing information.]*

8.5 Geriatric Use:
Based on available data, no adjustment of the dosage of BREO in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

Clinical trials of BREO for COPD included 2,508 subjects aged 65 and older and 564 subjects aged 75 and older. Clinical trials of BREO for asthma included 854 subjects aged 65 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

8.6 Hepatic Impairment*:*
Fluticasone furoate systemic exposure increased by up to 3-fold in subjects with hepatic impairment compared with healthy subjects. Hepatic impairment had no effect on vilanterol systemic exposure. Use BREO with caution in patients with moderate or severe hepatic impairment. Monitor patients for corticosteroid-related side effects *[see Clinical Pharmacology (12.3) of full prescribing information]*.

8.7 Renal Impairment:
There were no significant increases in either fluticasone furoate or vilanterol exposure in subjects with severe renal impairment (CrCl less than 30 mL/min) compared with healthy subjects. No dosage adjustment is required in patients with renal impairment *[see Clinical Pharmacology (12.3) of full prescribing information]*.

10 OVERDOSAGE
No human overdosage data has been reported for BREO. BREO contains both fluticasone furoate and vilanterol; therefore, the risks associated with overdosage for the individual components described below apply to BREO. Treatment of overdosage consists of discontinuation of BREO together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medicine can produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage.

10.1 Fluticasone Furoate:
Because of low systemic bioavailability (15.2%) and an absence of acute drug-related systemic findings in clinical trials, overdosage of fluticasone furoate is unlikely to require any treatment other than observation. If used at excessive doses for prolonged periods, systemic effects such as hypercorticism may occur *[see Warnings and Precautions (5.8)]*. Single- and repeat-dose trials of fluticasone furoate at doses of 50 to 4,000 mcg have been studied in human subjects. Decreases in mean serum cortisol were observed at dosages of 500 mcg or higher given once daily for 14 days.

10.2 Vilanterol:
The expected signs and symptoms with overdosage of vilanterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms of beta-adrenergic stimulation (e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, hyperglycemia, hypokalemia, metabolic acidosis). As with all inhaled sympathomimetic medicines, cardiac arrest and even death may be associated with an overdose of vilanterol.

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Asthma-Related Death
Inform patients with asthma that LABA, such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death and may increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Also inform them that currently available data are inadequate to determine whether concurrent use of ICS or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA.

Not for Acute Symptoms:
Inform patients that BREO is not meant to relieve acute symptoms of COPD or asthma and extra doses should not be used for that purpose. Advise patients to treat acute symptoms with an inhaled, short-acting $beta_2$-agonist such as albuterol. Provide patients with such medication and instruct them in how it should be used.

Instruct patients to seek medical attention immediately if they experience any of the following: decreasing effectiveness of inhaled, short-acting $beta_2$-agonists; need for more inhalations than usual of inhaled, short-acting $beta_2$-agonists; significant decrease in lung function as outlined by the physician.

Tell patients they should not stop therapy with BREO without physician/provider guidance since symptoms may recur after discontinuation.

Do Not Use Additional Long-acting $Beta_2$-agonists:
Instruct patients not to use other LABA for COPD and asthma.

Local Effects:
Inform patients that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing therapy with BREO, but at times therapy with BREO may need to be temporarily interrupted under close medical supervision. Advise patients to rinse the mouth with water without swallowing after inhalation to help reduce the risk of thrush.

Pneumonia:
Patients with COPD have a higher risk of pneumonia; instruct them to contact their healthcare providers if they develop symptoms of pneumonia.

Immunosuppression:
Warn patients who are on immunosuppressant doses of corticosteroids to avoid exposure to chickenpox or measles and, if exposed, to consult their physicians without delay. Inform patients of potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

Hypercorticism and Adrenal Suppression:
Advise patients that BREO may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, inform patients that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to BREO.

Reduction in Bone Mineral Density:
Advise patients who are at an increased risk for decreased BMD that the use of corticosteroids may pose an additional risk.

Ocular Effects:
Inform patients that long-term use of ICS may increase the risk of some eye problems (cataracts or glaucoma); consider regular eye examinations.

Risks Associated with Beta-agonist Therapy:
Inform patients of adverse effects associated with $beta_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

Hypersensitivity Reactions, Including Anaphylaxis:
Advise patients that hypersensitivity reactions (e.g., anaphylaxis, angioedema, rash, urticaria) may occur after administration of BREO. Instruct patients to discontinue BREO if such reactions occur.
There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder medications containing lactose; therefore, patients with severe milk protein allergy should not use BREO.

BREO ELLIPTA was developed in collaboration with Theravance

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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 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.

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 cuff-leak 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.

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.

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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 40-mg/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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Intensive ventilation precedes lesser complications

BY AMY KARON
Frontline Medical News

Addition of 10 cm H_2O 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% confidence interval, 1.2-2.8; $P = .003$), Dr. Leme and his associates reported.

The study comprised 320 adults who developed hypoxemia immediately 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

VIEW ON THE NEWS

High PEEP for all?

High 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).

H_2O, pressure-controlled ventilation, driving pressure of 15 cm H_2O, respiratory rate of 15/min, inspiratory time of 1.5 seconds, and 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_2O and 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_2O, and FIO_2 of 0.60, at a minimum respiratory rate that maintained $PaCO_2$ 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

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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.

Dexmedetomidine improves sedation in sepsis

BY AMY KARON
Frontline Medical News

Use 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

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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$_2$-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 dexmedetomidine. 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

A quarter of cultures were carbapenem-resistant

BY LUCAS FRANKI
Frontline Medical News

Nearly 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 at-risk 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.

Some abnormal findings may be underemphasized

BY JENNIE SMITH
Frontline Medical News

FROM CHEST

A 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.

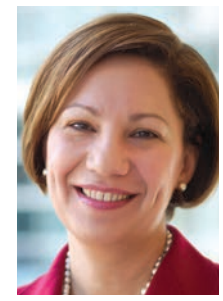
Dr. Mehta and colleagues noted in their analysis that Lung-RADS has not been studied prospectively in real practice settings and that the four cases – two of which involved delayed diagnosis – reveal "a significant limitation" of Lung-RADS.

"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 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.

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 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 recommendations 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

First 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

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VIEW ON THE NEWS

Refining prognosis with careful exam

STAS (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 one-third 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 high-grade 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.

EBUS scope, EUS-FNA similarly effective

BY DEEPAK CHITNIS
Frontline Medical News

In 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

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

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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-

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

A 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 hospitals, 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 screening, 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.

Bill would limit noneconomic damages to $250,000

BY ALICIA GALLEGOS
Frontline Medical News

New 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.


REP. GOODLATTE

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, criticized 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."


DR. SEGAL

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

BY MARY AGNES CAREY,
KAISER HEALTH NEWS

Despite 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.

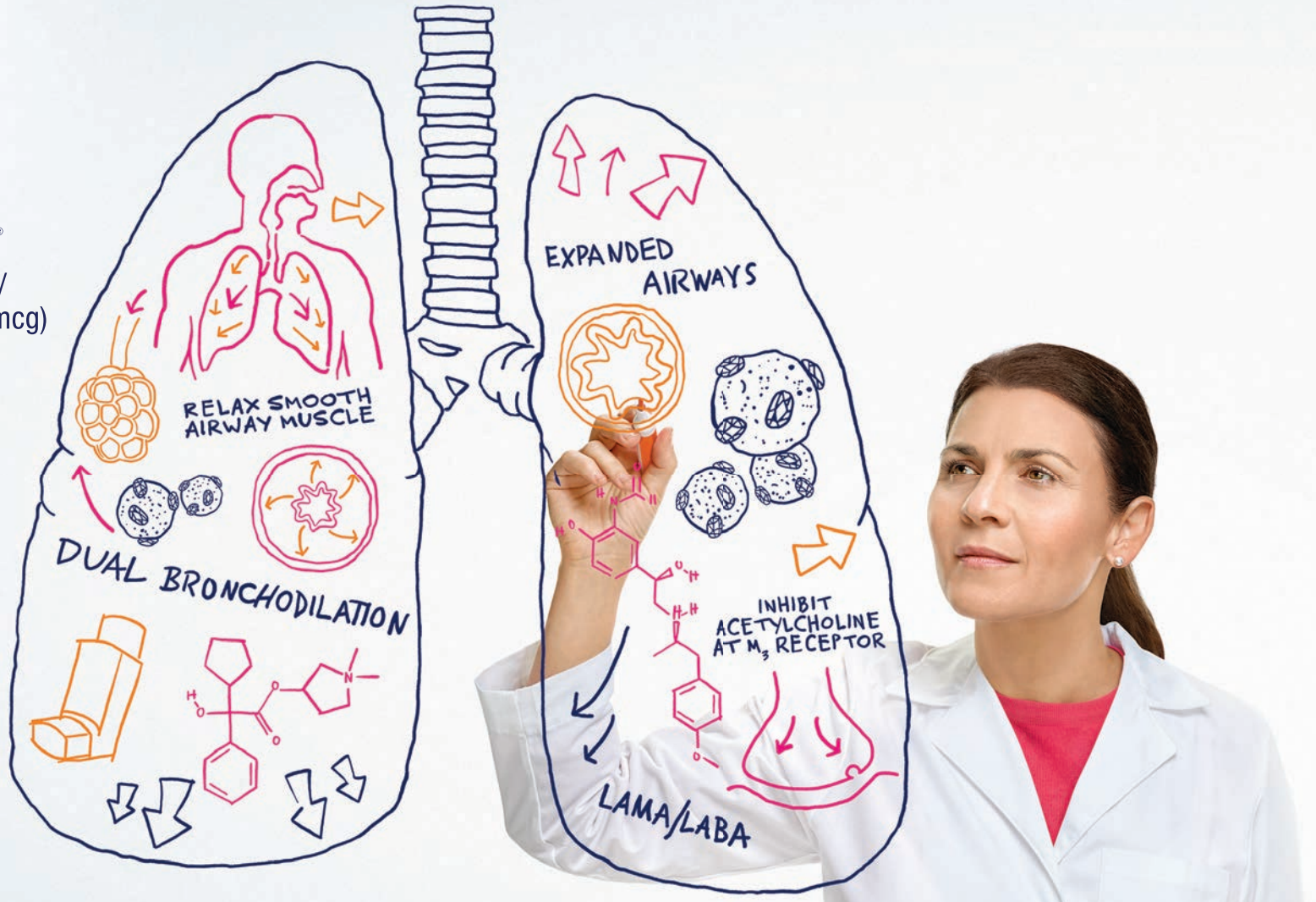
On the evening of March 23, Mr. Trump dispatched Office of Management and Budget Director Mick Mulvaney to tell his former House GOP colleagues that the president wanted a vote on March 24. It was time to move on to other priorities, including tax reform, he told House Republicans.

"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

BEVESPI AEROSPHERE®

(glycopyrrolate 9 mcg/
formoterol fumarate 4.8 mcg)
Inhalation Aerosol



BEVESPI AEROSPHERE is indicated for the maintenance treatment of COPD.

It is not indicated for the relief of acute bronchospasm or for the treatment of asthma.

Please see additional Important Safety Information and Brief Summary of Prescribing Information, including Boxed WARNING, on the adjacent pages.

IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING

WARNING: Long-acting $beta_2$-adrenergic agonists (LABAs), such as formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABAs, including formoterol fumarate.

The safety and efficacy of BEVESPI AEROSPHERE in patients with asthma have not been established. BEVESPI AEROSPHERE is not indicated for the treatment of asthma.

CONTRAINDICATION: All LABAs are contraindicated in patients with asthma without use of a long-term asthma control medication. BEVESPI is contraindicated in patients with a hypersensitivity to glycopyrrolate, formoterol fumarate, or to any component of the product.

WARNINGS AND PRECAUTIONS

- BEVESPI should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition
- BEVESPI should not be used for the relief of acute symptoms (ie, as rescue therapy for the treatment of acute episodes of bronchospasm). Acute symptoms should be treated with an inhaled short-acting $beta_2$-agonist
- BEVESPI should not be used more often or at higher doses than recommended, or with other LABAs, as an overdose may result
- If paradoxical bronchospasm occurs, discontinue BEVESPI immediately and institute alternative therapy
- If immediate hypersensitivity reactions, including angioedema, urticaria, or skin rash, occur, discontinue BEVESPI at once and consider alternative treatment
- BEVESPI can produce a clinically significant cardiovascular effect in some patients, as measured by increases in pulse rate, blood pressure, or symptoms. If such effects occur, BEVESPI may need to be discontinued
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines
- Be alert to hypokalemia and hyperglycemia
- Worsening of narrow-angle glaucoma or urinary retention may occur. Use with caution in patients with narrow-angle glaucoma, prostatic hyperplasia, or bladder-neck obstruction and instruct patients to contact a physician immediately if symptoms occur

ADVERSE REACTIONS: The most common adverse reactions with BEVESPI (≥2% and more common than

FOR THE MAINTENANCE TREATMENT OF COPD

DUAL BRONCHODILATION, DOWN TO A SCIENCE

INTELLIGENT FORMULATION*

Intelligent formulation for a pMDI using patented CO-SUSPENSION™ Delivery Technology[1]

MAXIMIZE BRONCHODILATION†

Improved lung function‡ vs placebo including[1]

- 150-mL improvement in predose FEV_1 at 24 weeks
- Nearly a 300-mL improvement in peak FEV_1 at 24 weeks
- Nearly a 200-mL improvement in FEV_1 at 5 minutes on Day 1

Adverse reactions with BEVESPI AEROSPHERE with a ≥2% incidence and more common than placebo were urinary tract infection and cough.[1]

BEVESPI AEROSPHERE is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms. It is not for the treatment of asthma.

*BEVESPI AEROSPHERE is a pMDI containing the LAMA glycopyrrolate and LABA formoterol fumarate, along with phospholipid porous particles that form the co-suspension with the micronized drug crystals.[1]

†Defined as superior improvement in lung function with BEVESPI AEROSPHERE vs its individual components and placebo in two 24-week pivotal trials.[1-3]

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placebo) were: cough, 4.0% (2.7%), and urinary tract infection, 2.6% (2.3%).

DRUG INTERACTIONS

- Use caution if administering additional adrenergic drugs because the sympathetic effects of formoterol may be potentiated
- Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of formoterol
- Use with caution in patients taking non–potassium-sparing diuretics, as the ECG changes and/or hypokalemia may worsen with concomitant $beta_2$-agonists
- The action of adrenergic agonists on the cardiovascular system may be potentiated by monoamine oxidase inhibitors, tricyclic antidepressants, or other drugs known to prolong the QTc interval. Therefore BEVESPI should be used with extreme caution in patients being treated with these agents
- Use beta-blockers with caution as they not only block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in patients with COPD
- Avoid co-administration of BEVESPI with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects

INDICATION: BEVESPI AEROSPHERE is a combination of glycopyrrolate, an anticholinergic, and formoterol fumarate, a long-acting $beta_2$-adrenergic agonist (LABA), indicated for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

LIMITATION OF USE: Not indicated for the relief of acute bronchospasm or for the treatment of asthma.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.

‡Demonstrated in two 24-week efficacy and safety studies in patients with moderate to very severe COPD (n=3699). The primary endpoint was change from baseline in trough FEV_1 at Week 24 for BEVESPI AEROSPHERE compared with placebo (150 mL), glycopyrrolate 18 mcg BID (59 mL), and formoterol fumarate 9.6 mcg BID (64 mL); results are from Trial 1; $P<0.0001$ for all treatment comparisons.[1,2] Statistically significant results were also seen in Trial 2.[1,3]

References: 1. BEVESPI AEROSPHERE [Package Insert]. Wilmington, DE: AstraZeneca; 2016. **2.** Data on File, 3236300, AZPLP. **3.** Data on File, 3236400, AZPLP.

AstraZeneca

BEVESPI AEROSPHERE™

(glycopyrrolate and formoterol fumarate) inhalation aerosol, for oral inhalation use

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABAs) increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABAs, including formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE.

The safety and efficacy of BEVESPI AEROSPHERE in patients with asthma have not been established. BEVESPI AEROSPHERE is not indicated for the treatment of asthma. *[see Warnings and Precautions (5.1) in the full Prescribing Information]*

INDICATIONS AND USAGE

BEVESPI AEROSPHERE is a combination of glycopyrrolate and formoterol fumarate indicated for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Important Limitation of Use: BEVESPI AEROSPHERE is not indicated for the relief of acute bronchospasm or for the treatment of asthma *[see Warnings and Precautions (5.1, 5.2) in the full Prescribing Information]*.

DOSAGE AND ADMINISTRATION

BEVESPI AEROSPHERE (glycopyrrolate/formoterol fumarate 9 mcg/4.8 mcg) should be administered as two inhalations taken twice daily in the morning and in the evening by the orally inhaled route only. Do not take more than two inhalations twice daily.

BEVESPI AEROSPHERE contains 120 inhalations per canister. The canister has an attached dose indicator, which indicates how many inhalations remain. The dose indicator display will move after every tenth actuation. When nearing the end of the usable inhalations, the color behind the number in the dose indicator display window changes to red. BEVESPI AEROSPHERE should be discarded when the dose indicator display window shows zero.

Priming BEVESPI AEROSPHERE is essential to ensure appropriate drug content in each actuation. Prime BEVESPI AEROSPHERE before using for the first time. To prime BEVESPI AEROSPHERE, release 4 sprays into the air away from the face, shaking well before each spray. BEVESPI AEROSPHERE must be re-primed when the inhaler has not been used for more than 7 days. To re-prime BEVESPI AEROSPHERE, release 2 sprays into the air away from the face, shaking well before each spray.

CONTRAINDICATIONS

All LABAs are contraindicated in patients with asthma without use of a long-term asthma control medication *[see Warnings and Precautions (5.1) in the full Prescribing Information]*. BEVESPI AEROSPHERE is not indicated for the treatment of asthma.

BEVESPI AEROSPHERE is contraindicated in patients with hypersensitivity to glycopyrrolate, formoterol fumarate, or to any component of the product *[see Warnings and Precautions (5.5) in the full Prescribing Information]*.

WARNINGS AND PRECAUTIONS

Asthma-Related Death

Data from a large placebo-controlled trial in subjects with asthma showed that LABAs may increase the risk of asthma-related death. Data are not available to determine whether the rate of death in patients with COPD is increased by LABAs.

A 28-week, placebo-controlled US trial comparing the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs. 3/13,179 in subjects treated with placebo; RR 4.37, 95% CI: 1.25, 15.34). The increased risk of asthma-related death is considered a class effect of LABAs, including formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE.

No trial adequate to determine whether the rate of asthma-related deaths is increased in patients treated with BEVESPI AEROSPHERE has been conducted. The safety and efficacy of BEVESPI AEROSPHERE in patients with asthma have not been established. BEVESPI AEROSPHERE is not indicated for the treatment of asthma.

Deterioration of Disease and Acute Episodes

BEVESPI AEROSPHERE should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. BEVESPI AEROSPHERE has not been studied in patients with acutely deteriorating COPD. The use of BEVESPI AEROSPHERE in this setting is inappropriate.

BEVESPI AEROSPHERE should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. BEVESPI AEROSPHERE has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled short-acting beta$_2$-agonist.

When beginning BEVESPI AEROSPHERE, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these medicines and use them only for symptomatic relief of acute respiratory symptoms. When prescribing BEVESPI AEROSPHERE, the healthcare provider should also prescribe an inhaled, short acting beta$_2$-agonist and instruct the patient on how it should be used. Increasing inhaled beta$_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If BEVESPI AEROSPHERE no longer controls the symptoms of bronchoconstriction, or the patient's inhaled, short-acting beta$_2$-agonist becomes less effective, or the patient needs more inhalations of short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dosage of BEVESPI AEROSPHERE beyond the recommended dose is not appropriate in this situation.

Excessive Use of BEVESPI and Use with Other Long-Acting Beta$_2$-Agonists

As with other inhaled medicines containing beta$_2$-agonists, BEVESPI AEROSPHERE should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing LABAs, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic medicines. Patients using BEVESPI AEROSPHERE should not use another medicine containing a LABA for any reason *[see Drug Interactions (7.1) in the full Prescribing Information]*.

Paradoxical Bronchospasm

As with other inhaled medicines, BEVESPI AEROSPHERE can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with BEVESPI AEROSPHERE, it should be treated immediately with an inhaled, short-acting bronchodilator, BEVESPI AEROSPHERE should be discontinued immediately, and alternative therapy should be instituted.

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions have been reported after administration of glycopyrrolate or formoterol fumarate, the components of BEVESPI AEROSPHERE. If signs suggesting allergic reactions occur, in particular, angioedema (including difficulties in breathing or swallowing, swelling of tongue, lips and face), urticaria, or skin rash, BEVESPI AEROSPHERE should be stopped at once and alternative treatment should be considered.

Cardiovascular Effects

Formoterol fumarate, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms *[see Clinical Pharmacology (12.2) in the full Prescribing Information]*. If such effects occur, BEVESPI AEROSPHERE may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown.

Therefore, BEVESPI AEROSPHERE should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Coexisting Conditions

BEVESPI AEROSPHERE, like all medications containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-agonist albuterol, when administered intravenously, have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis.

Hypokalemia and Hyperglycemia

Beta$_2$-agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects *[see Clinical Pharmacology (12.2) in the full Prescribing Information]*. The decrease in serum potassium is usually transient, not requiring supplementation. Beta$_2$-agonist medicines may produce transient hyperglycemia in some patients. In two clinical trials of 24-weeks and a 28-week safety extension study evaluating BEVESPI AEROSPHERE in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

Worsening of Narrow-Angle Glaucoma

BEVESPI AEROSPHERE should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

Worsening of Urinary Retention

BEVESPI AEROSPHERE should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

ADVERSE REACTIONS

LABAs, such as formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE, increase the risk of asthma-related death. BEVESPI AEROSPHERE is not indicated for the treatment of asthma *[see Boxed Warning and Warnings and Precautions (5.1) in the full Prescribing Information]*.

The following adverse reactions are described in greater detail elsewhere in the labeling:

- Paradoxical bronchospasm *[see Warnings and Precautions (5.4) in the full Prescribing Information]*
- Hypersensitivity reactions *[see Contraindications (4), Warnings and Precautions (5.5) in the full Prescribing Information]*
- Cardiovascular effects *[see Warnings and Precautions (5.6) in the full Prescribing Information]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.9) in the full Prescribing Information]*
- Worsening of urinary retention *[see Warnings and Precautions (5.10) in the full Prescribing Information]*

Clinical Trials Experience

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

The clinical program for BEVESPI AEROSPHERE included 4,911 subjects with COPD in two 24-week lung function trials, one long-term safety extension study of 28 weeks, and 10 other trials of shorter duration. A total of 1,302 subjects have received at least 1 dose of BEVESPI AEROSPHERE. The safety data described below are based on the two 24-week trials and the one 28-week long-term safety extension trial. Adverse reactions observed in the other trials were similar to those observed in these confirmatory trials.

24-Week Trials

The incidence of adverse reactions with BEVESPI AEROSPHERE in Table 1 is based on reports in two 24-week, placebo-controlled trials (Trials 1 and 2; n=2,100 and n=1,610, respectively). Of the 3,710 subjects, 56% were male and 91% were Caucasian. They had a mean age of 63 years and an average smoking history of 51 pack-years, with 54% identified as current smokers. At screening, the mean post-bronchodilator percent predicted forced expiratory volume in 1 second (FEV_1) was 51% (range: 19% to 82%) and the mean percent reversibility was 20% (range: -32% to 135%).

Subjects received one of the following treatments: BEVESPI AEROSPHERE, glycopyrrolate 18 mcg, formoterol fumarate 9.6 mcg, or placebo twice daily or active control.

Table 1 - Adverse Reactions with BEVESPI AEROSPHERE ≥2% Incidence and More Common than with Placebo in Subjects with Chronic Obstructive Pulmonary Disease

Adverse Reaction	BEVESPI AEROSPHERE (n=1036) %	Glycopyrrolate 18 mcg BID (n=890) %	Formoterol Fumarate 9.6 mcg BID (n=890) %	Placebo (n=443) %
Respiratory, thoracic, and mediastinal disorders				
Cough	4.0	3.0	2.7	2.7
Infections and infestation				
Urinary tract infection	2.6	1.8	1.5	2.3

Other adverse reactions defined as events with an incidence of >1% but less than 2% with BEVESPI AEROSPHERE but more common than with placebo included the following: arthralgia, chest pain, tooth abscess, muscle spasms, headache, oropharyngeal pain, vomiting, pain in extremity, dizziness, anxiety, dry mouth, fall, influenza, fatigue, acute sinusitis, and contusion.

Long-Term Safety Extension Trial

In a 28-week long-term safety extension trial, 893 subjects who successfully completed Trial 1 or Trial 2 were treated for up to an additional 28 weeks for a total treatment period of up to 52 weeks with BEVESPI AEROSPHERE, glycopyrrolate 18 mcg, formoterol fumarate 9.6 mcg administered twice daily or active control. Because the subjects continued from Trial 1 or Trial 2 into the safety extension trial, the demographic and baseline characteristics of the long-term safety extension trial were similar to those of the placebo-controlled efficacy trials described above. The adverse reactions reported in the long-term safety trial were consistent with those observed in the 24-week placebo-controlled trials.

Additional Adverse Reactions**:** Other adverse reactions that have been associated with the component formoterol fumarate include: hypersensitivity reactions, hyperglycemia, sleep disturbance, agitation, restlessness, tremor, nausea, tachycardia, palpitations, cardiac arrhythmias (atrial fibrillation, supraventricular tachycardia, and extrasystoles).

DRUG INTERACTIONS

No formal drug interaction studies have been performed with BEVESPI AEROSPHERE.

Adrenergic Drugs

If additional adrenergic drugs are to be administered by any route, they should be used with caution because the sympathetic effects of formoterol, a component of BEVESPI AEROSPHERE, may be potentiated *[see Warnings and Precautions (5.3) in the full Prescribing Information]*.

Xanthine Derivatives, Steroids, or Diuretics

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of $beta_2$ adrenergic agonists such as formoterol, a component of BEVESPI AEROSPHERE.

Non-Potassium Sparing Diuretics

The ECG changes and/or hypokalemia that may result from the administration of non-potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by $beta_2$-agonists, especially when the recommended dose of the $beta_2$-agonist is exceeded. Approximately 17% of subjects were taking non-potassium sparing diuretics during the two 24-week placebo-controlled trials in subjects with COPD. The incidence of adverse events in subjects taking non-potassium-sparing diuretics was similar between BEVESPI AEROSPHERE and placebo treatment groups. In addition, there was no evidence of a treatment effect on serum potassium with BEVESPI AEROSPHERE compared to placebo in subjects taking non-potassium sparing diuretics during the two 24-week trials. However, caution is advised in the coadministration of BEVESPI AEROSPHERE with non-potassium-sparing diuretics.

Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs

BEVESPI AEROSPHERE, as with other $beta_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants or other drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval may be associated with an increased risk of ventricular arrhythmias.

Beta-Blockers

Beta-adrenergic receptor antagonists (beta-blockers) and BEVESPI AEROSPHERE may interfere with the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of $beta_2$-agonists, but may produce severe bronchospasm in COPD patients. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Anticholinergics

There is a potential for an additive interaction with concomitantly used anticholinergic medications. Therefore, avoid coadministration of BEVESPI AEROSPHERE with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects *[see Warnings and Precautions (5.9, 5.10) and Adverse Reactions (6) in the full Prescribing Information]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects:

Pregnancy Category C. There are no adequate and well-controlled trials of BEVESPI AEROSPHERE or its individual components, glycopyrrolate and formoterol fumarate, in pregnant women. Because animal reproduction studies are not always predictive of human response, BEVESPI AEROSPHERE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women should be advised to contact their physicians if they become pregnant while taking BEVESPI AEROSPHERE.

Glycopyrrolate: There was no evidence of teratogenic effects in rats and rabbits at approximately 18,000 and 270 times, respectively, the maximum recommended human daily inhalation dose (MRHDID) in adults (on a mg/m^2 basis at a maternal oral dose of 65 mg/kg/day in rats and at a maternal intramuscular injection dose of 0.5 mg/kg in rabbits).

Single-dose studies in humans found that very small amounts of glycopyrrolate passed the placental barrier.

Formoterol Fumarate: Formoterol fumarate has been shown to be teratogenic, embryocidal, to increase pup loss at birth and during lactation, and to decrease pup weights in rats and teratogenic in rabbits. These effects were observed at approximately 1,500 (rats) and 61,000 (rabbits) times the MRHDID (on a mg/m^2 basis at maternal oral doses of 3 mg/kg/day and above in rats and 60 mg/kg/day in rabbits). Umbilical hernia was observed in rat fetuses at approximately 1,500 times the MRHDID (on a mg/m^2 basis at maternal oral doses of 3 mg/kg/day and above). Prolonged pregnancy and fetal brachygnathia was observed in rats at approximately 7600 times the MRHDID (on a mg/m^2 basis at an oral maternal dose of 15 mg/kg/day in rats). In another study in rats, no teratogenic effects were seen at approximately 600 times the MRHDID (on a mg/m^2 basis at maternal inhalation doses up to 1.2 mg/kg/day in rats).

Subcapsular cysts on the liver were observed in rabbit fetuses at an oral dose approximately 61,000 times the MRHDID (on a mg/m^2 basis at a maternal oral dose of 60 mg/kg/day in rabbits). No teratogenic effects were observed at approximately 3600 times the MRHDID (on a mg/m^2 basis at maternal oral doses up to 3.5 mg/kg/day).

Labor and Delivery

There are no well-controlled human trials that have investigated the effects of BEVESPI AEROSPHERE on preterm labor or labor at term. Because $beta_2$-agonists may potentially interfere with uterine contractility, BEVESPI AEROSPHERE should be used during labor only if the potential benefit justifies the potential risk.

Nursing Mothers

It is not known whether BEVESPI AEROSPHERE is excreted in human milk. Because many drugs are excreted in human milk and because formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE, has been detected in the milk of lactating rats, caution should be exercised when BEVESPI AEROSPHERE is administered to a nursing woman. Since there are no data from controlled trials on the use of BEVESPI AEROSPHERE by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue BEVESPI AEROSPHERE, taking into account the importance of BEVESPI AEROSPHERE to the mother.

Pediatric Use

BEVESPI AEROSPHERE is not indicated for use in children. The safety and effectiveness of BEVESPI AEROSPHERE in the pediatric population have not been established.

Geriatric Use

Based on available data, no adjustment of the dosage of BEVESPI AEROSPHERE in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

The confirmatory trials of BEVESPI AEROSPHERE for COPD included 1,680 subjects aged 65 and older and, of those, 290 subjects were aged 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Hepatic Impairment

Formal pharmacokinetic studies using BEVESPI AEROSPHERE have not been conducted in patients with hepatic impairment. However, since formoterol fumarate is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of formoterol fumarate in plasma. Therefore, patients with hepatic disease should be closely monitored.

Renal Impairment

Formal pharmacokinetic studies using BEVESPI AEROSPHERE have not been conducted in patients with renal impairment. In patients with severe renal impairment (creatinine clearance of ≤30 mL/min/1.73 m^2) or end-stage renal disease requiring dialysis, BEVESPI AEROSPHERE should be used if the expected benefit outweighs the potential risk *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

OVERDOSAGE

No cases of overdose have been reported with BEVESPI AEROSPHERE. BEVESPI AEROSPHERE contains both glycopyrrolate and formoterol fumarate; therefore, the risks associated with overdosage for the individual components described below apply to BEVESPI AEROSPHERE. Treatment of overdosage consists of discontinuation of BEVESPI AEROSPHERE together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. Cardiac monitoring is recommended in case of overdosage.

Glycopyrrolate

High doses of glycopyrrolate, a component of BEVESPI AEROSPHERE, may lead to anticholinergic signs and symptoms such as nausea, vomiting, dizziness, lightheadedness, blurred vision, increased intraocular pressure (causing pain, vision disturbances or reddening of the eye), obstipation or difficulties in voiding. However, there were no systemic anticholinergic adverse effects following single inhaled doses up to 144 mcg in subjects with COPD.

Formoterol Fumarate

An overdose of formoterol fumarate would likely lead to an exaggeration of effects that are typical for $beta_2$-agonists: seizures, angina, hypertension, hypotension, tachycardia, atrial and ventricular tachyarrhythmias, nervousness, headache, tremor, palpitations, muscle cramps, nausea, dizziness, sleep disturbances, metabolic acidosis, hyperglycemia, hypokalemia. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of formoterol fumarate.

Manufactured for: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

By: Aventis Pharma LTD, Holmes Chapel CW48BE, United Kingdom

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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.

FRANCK REPORTER/THINKSTOCK

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.

Hospitalizations fell after rotavirus vaccine, PCVs

BY DAN WATSON
Frontline Medical News

Vaccination 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 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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VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: These two articles represent the importance of vaccinations and their impact on the health of children worldwide. It is important to advocate locally and on a national level, no matter what the political climate is, for improvement in vaccination rates and vaccine research.

Unvaccinated first hit in pertussis outbreak

BY LUCAS FRANKI
Frontline Medical News

During 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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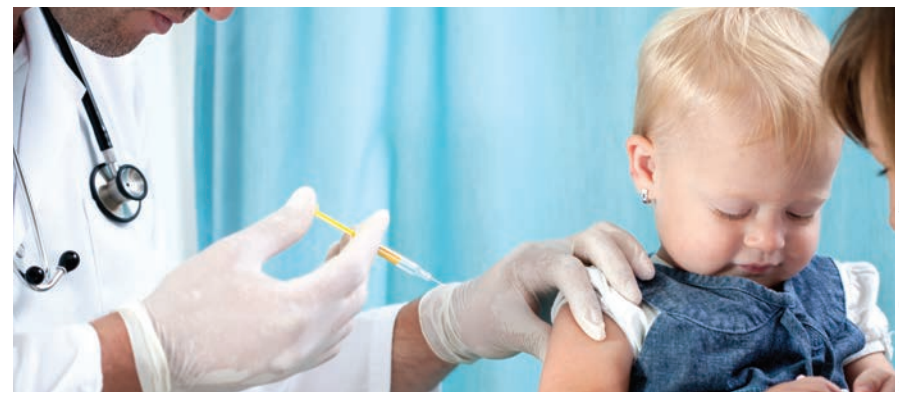


KATARZYNABIALASIEWICZ/THINKSTOCK

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.

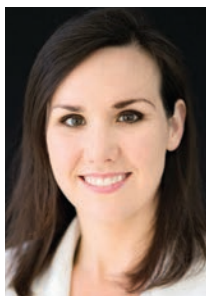
As bacteremia caused by pneumococci decreased, 77% of cases in the post-PCV13 time period were caused by *Escherichia coli, Salmonella spp.*, and *Staphylococcus aureus*. "A total of 76% of bacteremia occurred with a source, including 34% urinary tract infections, 17% gastroenteritis, 8% pneumonias, 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.

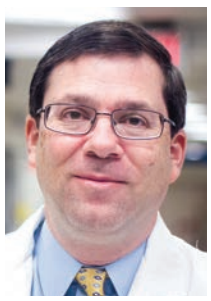
CRITICAL CARE COMMENTARY: Sepsis resuscitation in a post-EGDT age

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

Critical 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 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, 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.



DR. HEAD



DR. COOPERSMITH

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 $ScvO_2$ was not 70% or greater, patients were transfused until their hematocrit was greater than 30%, and, if this still did not bring their $ScvO_2$ 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.

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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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% 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 $ScvO_2$ 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 $ScvO_2$ 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 $ScvO_2$. 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 $ScvO_2$, 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

We 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

Sandra 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.

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

Endobronchial 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.[1] 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.[2] 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.[3] 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 effectiveness of EBUS-TBNA improves with increasing number of procedures performed, allowing for access to a greater number of lymph nodes without 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

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.[4,5] 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

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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.[6] 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

that regulations protect the patient.

Without question, EBUS bronchoscopy 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 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 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.

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.

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

Dr. 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

This month in *CHEST*: Editor's picks

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

Original Research

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)

Giants in Chest Medicine

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.

Management of Children With Chronic Wet Cough and Protracted Bacterial Bronchitis: CHEST Guideline and Expert Panel Report. By Dr. A. B. Chang, et al; on behalf of the CHEST Expert Cough Panel.

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.

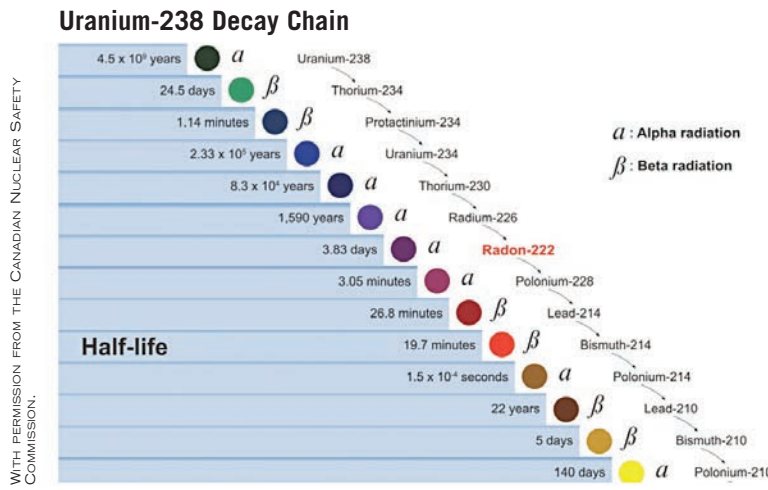
Occupational control of exposure to radon and radon progeny is accomplished primarily by ventilation. In high-grade deposits of uranium, such as the 20% ore grades in the Athabasca Basin of Saskatchewan, remote control mining is performed.

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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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_2) 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 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_2 maintained between 70-100 mm Hg or SpO_2 between 94-98%) vs standard care group (permitting PaO_2 values up to 150 mm Hg or SpO_2 values between 97-100%) in ICU patients admitted for at least 72 hours (Girardis et al. *JAMA.* 2016;316[15]:1583). There were striking differences in ICU 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.

DR. KAUR

DR. BOWTON

Complementing the findings of Girardis and colleagues, a recent analysis of more than 14,000 critically ill patients, found that time spent at $PaO_2 > 200$ 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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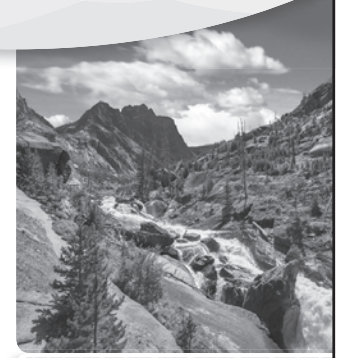

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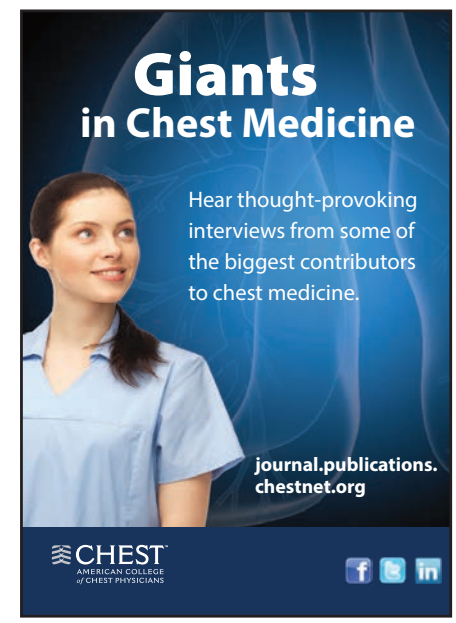

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Based on current evidence, it seems appropriate to maintain physiologically normal levels of PaO_2 without causing hyperoxia in critically ill patients. Oxygen saturation greater than 97% or 98% for prolonged periods should be avoided. Further randomized 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 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).


DR. JOHNSON

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 benefits of treating sleep-disordered breathing in specific patient subsets, many physicians may start to question, "Why all the fuss?" The Sleep NetWork is bringing the leaders in the 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!


DR. DAS

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.

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!

CHEST® Annual Meeting 2017

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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.

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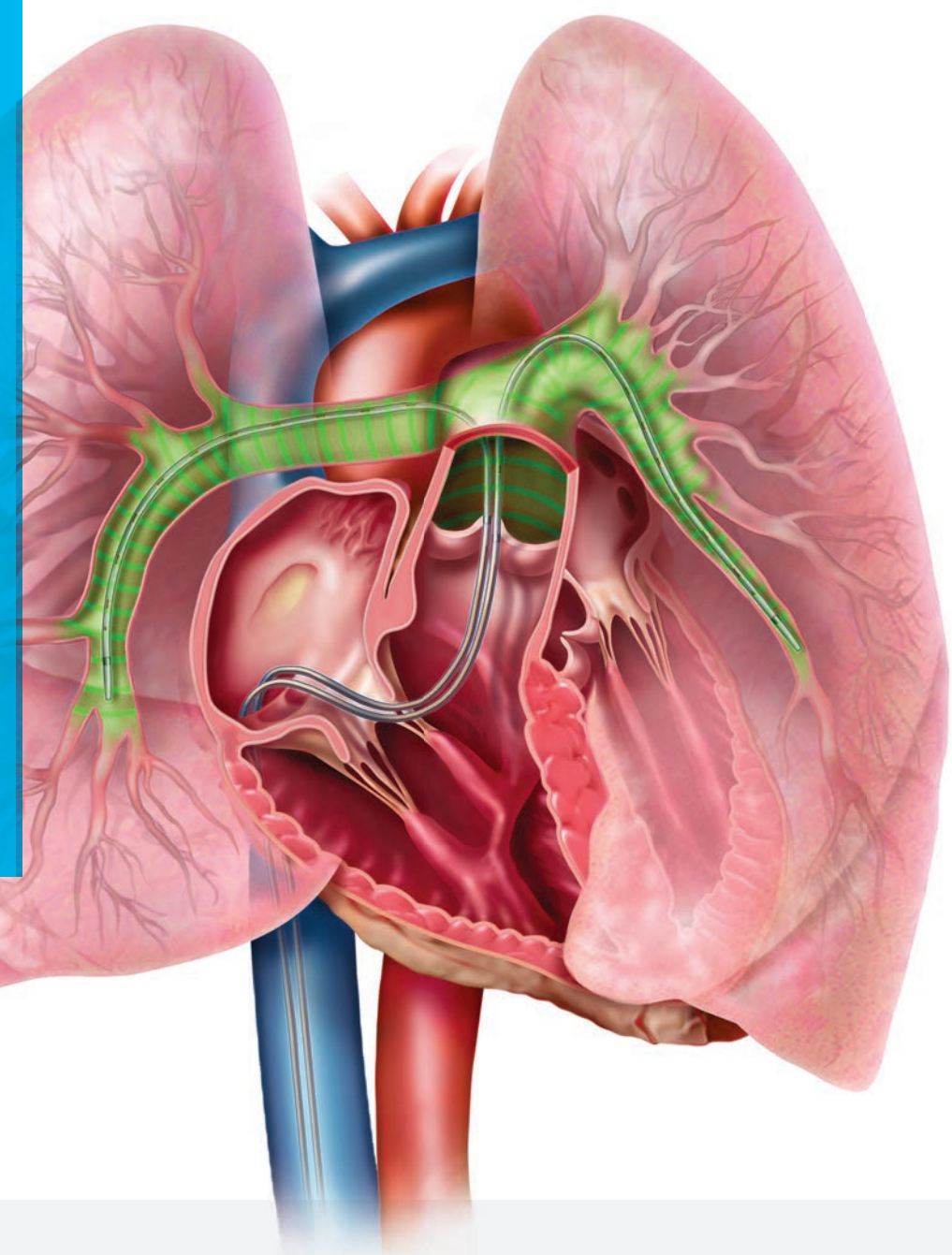

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2 *Braaten, J et al., Thromb Haemost 1997;78:1063-8; Francis, C et al. Ultrasound in Medicine and Biology 1995; 21(3):419-424; Soltani, A et al., Physics in Medicine and Biology 2008; 53:6837-6847*

3 *Kucher, N., et al., Circulation, Vol. 129, No. 4, 2014, 479–486.*

4 *Piazza, G., et al., American College of Cardiology 63rd Annual Scientific Session, Wash D.C., March 30, 2014.*

FDA CLEARED INDICATIONS: The EkoSonic® 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.ekoscorp.com. Caution: Federal (USA) law restricts these devices to sale by or on the order of a physician. **THE CE MARK (CE0086) HAS BEEN AFFIXED TO THE EKOSONIC® PRODUCT WITH THE FOLLOWING INDICATIONS:** ***Peripheral Vasculature:*** The EkoSonic® Endovascular Device, consisting of the Intelligent Drug Delivery Catheter (IDDC) and the MicroSonic™ Device (MSD), is intended for controlled and selective infusion of physician-specified fluids, including thrombolytics, into the peripheral vasculature. All therapeutic agents utilized with the EkoSonic® Endovascular System should be fully prepared and used according to the instruction for use of the specific therapeutic agent. ***Pulmonary Embolism:*** The EKOS EkoSonic® Endovascular System is intended for the treatment of pulmonary embolism patients with ≥ 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 ≥ 25mmHg) or echocardiographic evaluation.

BTG

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