Celebrating 10 Years
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FRONTLINE MEDICAL NEWS

"We are going to have to rewrite the guidelines and change our algorithms," Dr. Jadwiga Wedzicha predicted.

LABA-LAMA bests LABA-steroid in COPD

BY SUSAN LONDON
Frontline Medical News

SAN FRANCISCO – It may be time to revise guidelines for treatment of chronic obstructive pulmonary disease (COPD) complicated by exacerbations, based on data from a phase III trial reported at an international conference of the American Thoracic Society.

The trial, known as FLAME, undertook a head-to-head comparison of two inhaled drug combinations in more than 3,300 patients from 43 countries. Patients were randomized to once-daily indacaterol (a long-acting beta-agonist, or LABA, bronchodilator) and glycopyrronium (a long-acting muscarinic antagonist, or LAMA, bronchodilator), or to twice-daily salmeterol, also a LABA bronchodilator, and the inhaled glucocorticoid fluticasone.

After a year, the annual rate of COPD exacerbations was 11% lower with indacaterol-glycopyrronium than with salmeterol-fluticasone, according to results reported in a press conference and simultaneously published (N Engl J Med. 2016 May 15. doi: 10.1056/NEJMoa1516385). The difference not only met

See **COPD** • *page 7*

CPAP protective in mild stroke patients with sleep apnea

Fewer recurrent vascular events.

BY BRUCE JANCIN
Frontline Medical News

DENVER – Long-term continuous positive airway pressure (CPAP) for treatment of sleep apnea in patients with a recent mild stroke or transient ischemic attack resulted in improved cardiovascular and metabolic risk factors, better neurologic function, and a reduction in the recurrent vascular event rate, compared with usual care in the SLEEP TIGHT study.

"Up to 25% of patients will have a stroke, cardiovascular event, or death within 90 days after a minor stroke or TIA [transient ischemic attack] despite current preventive strategies. And, importantly, patients with a TIA or stroke have a high prevalence of obstructive sleep apnea – on the order of 60%-80%," explained Dr. H. Klar Yaggi at the annual meeting of the Associated Professional Sleep Societies.

SLEEP TIGHT's findings support the hypothesis that diagnosis and treatment of sleep apnea in patients with a recent minor stroke or TIA will address a major unmet need for better methods of reducing the high vascular risk present in this population, said Dr.

See **SLEEP TIGHT** • *page 6*

INSIDE

Helmet cut intubation rate in ARDS

BY HEIDI SPLETE
Frontline Medical News

Treating acute respiratory distress syndrome patients with helmets instead of face masks reduced intubation and 90-day mortality rates, based on data from a randomized trial of 83 adults published in JAMA.

Intubation incidence was 18% in 44 patients treated with helmets, compared with 62% for 39 patients treated with face masks. In addition, patients in the helmet group had significantly more ventilator-free days than the mask group (28 vs. 13; *P* less than .001), and both hospital mortality and 90-day mortality rates were significantly lower in the helmet group compared to the mask group (27% vs. 49%; *P* = .04 and 34% vs. 56%; *P* = .02, respectively)

Adverse event rates were rare and similar between the helmet and mask groups. Three interface-related skin ulcers occurred in each group; nose ulcers in 7% of the mask group and neck ul-

See **NIV** • *page 7*

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  - —**2.3× as many patients on Esbriet maintained their baseline function at 52 weeks** vs placebo (23% vs 10% of patients; 13% absolute difference; *P*<0.001)
- **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]**
- Safety and efficacy were evaluated in three phase 3, double-blind, placebo-controlled, multicenter trials in 1247 patients randomized to receive Esbriet (n=623) or placebo (n=624)[2]

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  - —eg, elevated liver enzymes, gastrointestinal events, and photosensitivity reactions or rash

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Elevated liver enzymes: Increases in ALT and AST >3× ULN have been reported in patients treated with Esbriet. Rarely these have been associated with concomitant elevations in bilirubin. Patients treated with Esbriet had a higher incidence of elevations in ALT or AST than placebo patients (3.7% vs 0.8%, respectively). No cases of liver transplant or death due to liver failure that were related to Esbriet have been reported. However, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that could lead to death or the need for liver transplants in some patients. Conduct liver function tests (ALT, AST, and bilirubin) prior to initiating Esbriet, then monthly for the first 6 months and every 3 months thereafter. Dosage modifications or interruption may be necessary.

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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Please see Brief Summary of Prescribing Information on adjacent pages for additional Important Safety Information.

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®
(pirfenidone) capsules 267 mg

Lebrikizumab boosts lung function in asthma

BY BRUCE JANCIN
Frontline Medical News

LOS ANGELES – The investigational interleukin-13 inhibitor lebrikizumab provides a clinically meaningful improvement in measures of lung function within 1 week after the first dose in patients with moderate-to-severe uncontrolled asthma on standard-of-care therapy and a high baseline serum periostin level, Dr. Jonathan Corren reported at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

He presented a post hoc analysis of three phase II randomized trials of lebrikizumab as add-on therapy in a total of 558 patients with uncontrolled asthma while on a moderate- or high-dose inhaled corticosteroid plus at least one other controller medication, most often a long-acting beta agonist. The post hoc analysis included 333

asthma patients who received lebrikizumab subcutaneously at 125 or 250 mg every 4 weeks for 12 weeks and 225 who got placebo.

Baseline serum periostin levels were 50 ng/mL or higher in 252 participants.

One week after the first dose of lebrikizumab, the high serum periostin group demonstrated a placebo-subtracted mean 147-mL improvement from baseline in pre-bronchodilator FEV_1.

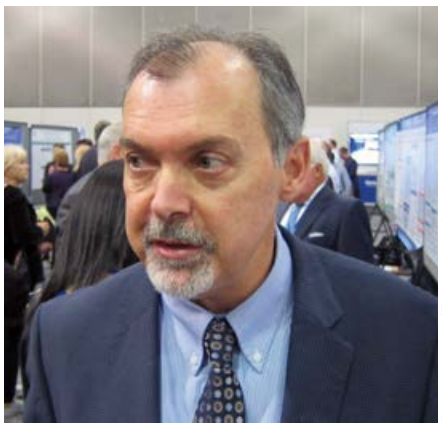
The week 1 improvement in FEV_1 with lebrikizumab in the low serum periostin group was more modest: a placebo-subtracted 57 mL.

The response to lebrikizumab was maintained through 12 weeks of once-monthly therapy, with a mean placebo-subtracted week 12 improvement in FEV_1 of 198 mL in the high-periostin group, compared with 74 mL in low-periostin patients. The lebrikizumab-treated group with high baseline periostin had a 16% improvement from baseline in FEV_1 as compared with a 5% improvement in placebo-treated patients with high periostin.

The three trials were known by the acronyms MILLY, LUTE, and VERSE. Dr. Corren was first author of the MILLY study (N Engl J Med. 2011 Sep 22;365(12):1088-98).

MILLY was the initial report that lebrikizumab performed markedly better in patients with uncontrolled asthma and a high baseline serum periostin – a biomarker for IL-13 activity – and that periostin was a better predictor of response to lebrikizumab than either blood eosinophil count or serum IgE, said Dr. Corren of the University of California, Los Angeles.

Lebrikizumab is an IgG4 humanized monoclonal antibody that binds



Bruce Jancin/Frontline Medical News

The lebrikizumab-treated group with high baseline periostin had a 16% improvement from baseline in FEV_1, Dr. Corren said.

to IL-13 with high affinity. Its efficacy in the phase II trials confirms the importance of IL-13 as a mediator of disease activity in a subset of asthma patients with activation of Type 2 lymphocytes.

"We know specifically that IL-13 has some very important effects in asthma, including upregulation of adhesion molecules that allow eosinophils to stick in the lung, as well as promoting hyperplasia of smooth muscle and mucus cell hyperplasia with increased mucus secretion.

Immunologically, it allows switching from IgM to IgE on the surface of B cells. So IL-13 is a cytokine that literally makes people atopic," Dr. Corren explained in an interview.

Several ongoing phase III randomized trials of lebrikizumab in adults with uncontrolled asthma despite standard-of-care therapy are due to be completed in the first half of 2017.

Dr. Corren reported receiving research funding from Roche/Genentech, which sponsored the studies.

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CPAP reduced vascular events

SLEEP TIGHT *from page 1*

Yaggi, of Yale University in New Haven, Conn.

SLEEP TIGHT was a National Heart, Lung, and Blood Institute–sponsored phase II, 12-month, multicenter, single-blind, randomized, proof-of-concept study. It included 252 patients, 80% of whom had a recent minor stroke, the rest a TIA. These were patients with high levels of cardiovascular risk factors: two-thirds had hypertension, half were hyperlipidemic, 40% had diabetes, 15% had a prior MI, 10% had atrial fibrillation, and the group's mean body mass index was 30 kg/m^2.

Polysomnography revealed that 76% of subjects had sleep apnea as defined by an apnea-hypopnea index of at least 5 events per hour. In fact, they averaged about 23 events per hour, putting them in the moderate-severity range. As is common among stroke/TIA patients with sleep apnea, they experienced less daytime sleepiness than is typical in a sleep clinic population, with a mean baseline Epworth Sleepiness Scale score of 7.

Participants were randomized to one of three groups: a usual care control group, a CPAP arm, or an enhanced CPAP arm. The enhanced intervention protocol was designed to boost CPAP adherence; it included targeted education, a customized cognitive intervention, and additional CPAP support beyond the standard CPAP protocols used in sleep medicine clinics. Patients with sleep apnea in the two intervention arms were then placed on CPAP.

At 1 year of follow-up, the stroke rate was 8.7 per 100 patient-years in the usual care group, compared with 5.5 per 100 person-years in the combined intervention arms. The composite cardiovascular event rate, composed of all-cause mortality, acute MI, stroke, hospitalization for unstable angina, or urgent coronary revascularization, was 13.1 per 100 person-years with usual care and 11.0 in the CPAP intervention arms. While these results are encouraging, SLEEP TIGHT wasn't powered to show significant differences in these hard events.

In the CPAP arms, 58% had a NIH Stroke Scale score of 0-1, compared with 38% of the usual care group.

DR. YAGGI

Outcomes across the board didn't differ significantly between the CPAP and enhanced CPAP groups. And since the mean number of hours of CPAP use per night was also similar in the two groups – 3.9 hours with standard CPAP and 4.3 hours with enhanced CPAP – it's likely that the phase III trial will rely upon the much simpler standard CPAP intervention, according to Dr. Yaggi.

He deemed CPAP adherence in this stroke/TIA population to be similar to the rates typically seen in routine sleep medicine practice. Roughly 40% of the stroke/TIA patients were rated as having good adherence, 30% made some use of the therapy, and 30% had no or poor adherence. Nonetheless, patients in the two intervention arms did significantly better than the usual care group in terms of 1-year changes in insulin resistance and glycosylated hemoglobin. They also had lower 24-hour mean systolic blood pressure and were more likely to convert to a favorable pattern of nocturnal blood pressure dipping. However, no differences between the intervention and usual care groups were seen in levels of high-sensitivity C-reactive protein and interleukin-6.

Fifty-eight percent of patients in the intervention arms ended up with a desirable National Institutes of Health Stroke Scale score of 0-1, compared with 38% of the usual care group. Additionally, daytime sleepiness was reduced at last follow-up to a significantly greater extent in the CPAP groups, Dr. Yaggi noted. Greater CPAP use was associated with a favorable trend for improvement in the modified Rankin score, a measure of functional ability: a 0.3-point reduction with no or poor CPAP use, a 0.4-point decrease with some use, and a 0.9-point reduction with good use.

The encouraging results will be helpful in designing a planned much larger, event-driven, definitive phase III trial, Dr. Yaggi said.

Dr. Yaggi had no financial conflicts regarding this National Heart, Lung and Blood Institute-sponsored study.

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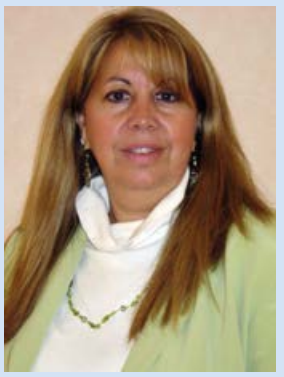

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Helmets cut intubation rates

NIV *from page 1*

cers in 7% of the helmet group.

The study population included adults aged 18 years and older who were admitted to the ICU at the University of Chicago between September 2012 and September 2015 and required face mask NIV.

The most common causes of acute respiratory failure in both patient groups were pneumonia and pneumonia that was caused by immunosuppression.

The study results were limited by several factors including a lack of blinding, the need for a learning curve for clinicians using the helmet, and the potential for patient-ventilator dyssynchrony in the helmet group, noted Dr. Bhakti K. Patel of the University of Chicago and her colleagues (JAMA 2016;315:2435-41).

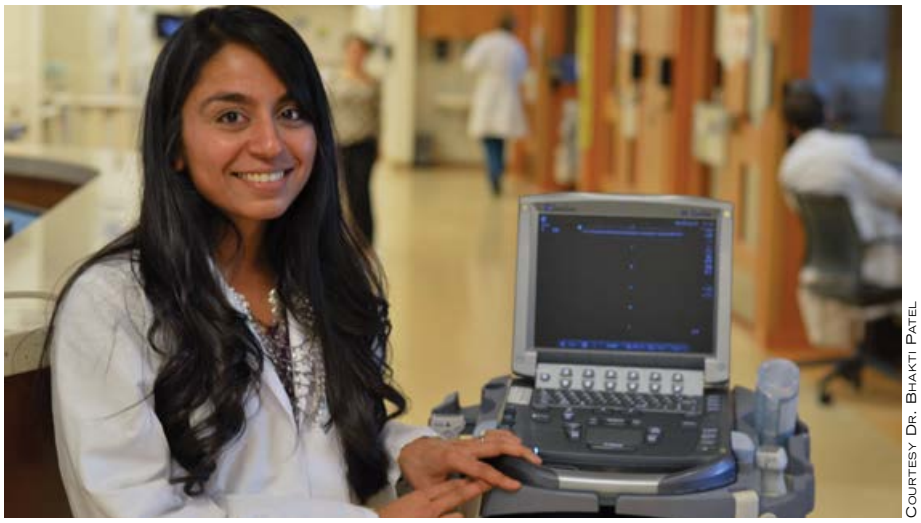
Multicenter studies are needed to support the findings, they added. However, the findings "affirm the far-reaching benefits of spontaneous yet highly supported ventilation in an awake, animated patient over invasive medical ventilation via endotracheal tube," they wrote.

"These findings warrant further investigation of helmet NIV for patients with ARDS and other types of AHRF [acute hypoxemic respiratory failure], particularly with attention to long-term outcomes," the researchers wrote.

The researchers had no financial conflicts to disclose.

In a related study published in the Journal of Cardiothoracic and Vascular Anesthesia, patients treated with noninvasive positive pressure ventilation (NPPV) through helmets had significantly lower heart rates, lower average arterial pressure, and improved left ventricular ejection fraction at the end of treatment, compared with patients treated with ventilation masks and controls. Dr. Yi Yang of Capital Medical University in Beijing, China, and colleagues conducted the prospective study of 75 adults experiencing hypoxemia within 24 hours of extubation after Stanford type A aortic dissection. The participants were divided into three 25-patient groups. The control group was treated with high-flux inhalation of oxygen via a Venturi mask, another group was treated with NPPV via a mask, and the third group was treated with NPPV via a helmet. (J Card Vasc Anesth. 2016. http://dx.doi.org/10.1053/j.jvca.2016.03.129).

The study was funded by China's public welfare industry of health.



COURTESY DR. BHAKTI PATEL

The long-term outcomes of helmet NIV for patients with ARDS and other types of acute hypoxemic respiratory failure need to be studied, said Dr. Patel.

VIEW ON THE NEWS

More research needed on helmet NIV

Dr. Eric J. Gartman, FCCP, comments: While we all got a good laugh at the [appearance of the] helmet itself, this study certainly produced very impressive results. This study is important, because if there is a way to improve the compliance and efficacy of noninvasive ventilation, and, thus, yielding the multiple benefits of avoiding endotracheal intubation and prolonged mechanical ventilation, it should be aggressively implemented.

The proposed mechanism for improved efficacy of these helmets is the preservation of applied pressures and avoidance of air leak. If the helmets do allow clinicians both to be able to increase airway pressures above levels they typically would with mask-NIV and maintain those pressures without unpredictable system leak, that would be of great physiologic importance for patients with acute respiratory failure.

While the results of this study are very impressive, it is a single-center study. Obviously, a larger multicenter trial, with all types of institutions included - not just large academic centers - would be helpful to elucidate the benefits of this technique and support a change in the standard of care in the use of NIV.

A change to this system would be a very large culture shift in NIV, and would mean a significant amount of training [for physician, nursing, and respiratory care professionals], purchasing the helmets, and ensuring that it is implemented properly and safely. As stated by the authors, this fact is similar to the change the occurred originally with NIV - but if their results reflect a true benefit over FM-NIV, such a large change would certainly be worth the effort.

FRONTLINE MEDICAL NEWS

"I'd like to see (these results) replicated, because in the U.S., for example, this medication isn't even available," said Dr. David Mannino, FCCP.

Annual exacerbation rate lower

COPD *from page 1*

the trial's primary endpoint of noninferiority, but also established superiority.

The dual bronchodilator combination was also superior to salmeterol-fluticasone when it came to other outcomes, such as respiratory-related health status and rescue medication use, and it had a good safety profile.

"I think we can say that... a dual bronchodilator is the first-choice combination that can be used in patients with COPD," commented lead author Dr. Jadwiga A. Wedzicha, a professor of respiratory medicine at the National Heart and Lung Institute, Imperial College London.

"This has a lot of implications. We are going to have to rewrite the guidelines and change our algorithms," she said, noting that a LABA with an inhaled corticosteroid (the latter of which has adverse effects, especially in an aging population) or single-agent LAMA is currently recommended. "I'm pretty convinced by the data. We've got basically four LABA-LAMAs out there; we need to see other studies and look at different patient populations. But I think the data is pretty persuasive, so that we can now change our algorithms."

Several ongoing studies are looking at triple therapy of a LABA-LAMA plus an inhaled corticosteroid, which may be useful in patients who continue to

Continued on page 10

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- Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. Do not exceed the recommended dose

References: 1. ProAir RespiClick Prescribing Information. Horsham, PA: Teva Respiratory, LLC; April 2016. **2.** ProAir RespiClick Patient Information Leaflet. Horsham, PA: Teva Respiratory, LLC; April 2016.

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Important Safety Information (continued)

- Immediate hypersensitivity reactions may occur. Discontinue ProAir RespiClick® immediately
- ProAir RespiClick® may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation
- Potential drug interactions can occur with beta-blockers, diuretics, digoxin, or monoamine oxidase inhibitors, and tricyclic antidepressants
- In controlled studies of ProAir RespiClick® in patients 12 years of age and older, adverse events that occurred at an incidence rate of at least 1% and greater than placebo included back pain (2% vs 1%), pain (2% vs <1%), gastroenteritis viral (1% vs <1%), sinus headache (1% vs <1%), and urinary tract infection (1% vs <1%)
- In controlled studies of ProAir RespiClick® in patients 4 to 11 years of age, adverse events that occurred at an incidence rate of at least 2% and greater than placebo included nasopharyngitis (2% vs 1%), oropharyngeal pain (2% vs 1%), and vomiting (3% vs 1%)

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Continued from page 7

have exacerbations on dual bronchodilator therapy, according to Dr. Wedzicha. "I think we'll move to the triple [therapy], because breathlessness is a problem," she predicted, noting that bronchodilators address that symptom well. "As you get more severe, you are going to get short of breath. So I think the LABA-LAMA will stay and the inhaled corticosteroid will be added on top. That's what I think COPD treatment will look like."

Press conference moderator Dr. David Mannino, professor & chair (Preventive Medicine & Environmental Health) at the University of Kentucky College of Public Health in Lexington, praised the research but disagreed about its implications. "I think one very good study is just that – one very good study. Is that enough to change guidelines? I don't think so," he said in an interview. "I'd like to see this replicated, because in the U.S., for example, this medication isn't even available. And if I write [a prescription] for one LABA-LAMA, what a patient actually gets may be dictated by their insurance and coverage and other things."

"So I would like to see this done with other LABA-LAMAs, and see other head-to-head trials," he elab-

orated. "And there is a great deal of boldness and risk on the part of drug companies to do head-to-head trials because they might not get a win. They lucked out in this one. You could do the same trial with products from different companies and not get the same results. And then you are left wondering what was wrong."

The 3,362 patients in FLAME had disabling, symptomatic COPD and had experienced at least one exacerbation in the past year. They were randomized evenly to once-daily indacaterol-glycopyrronium (marketed outside the United States) or twice-daily salmeterol-fluticasone.

Results showed that the annual rate of any exacerbation was significantly lower with indacaterol-glycopyrronium than with salmeterol-fluticasone in the per protocol population (3.59 vs. 4.03; rate ratio, 0.89), with similar findings in the intent-to-treat population. Additionally, in a preplanned analysis, the findings were consistent regardless of patients' blood levels of eosinophils, a possible marker of steroid sensitivity.

Indacaterol-glycopyrronium was also associated with a longer time to first exacerbation (71 vs. 51 days; hazard ratio, 0.84) and a lower annual rate of moderate or severe exacerbations (0.98 vs. 1.19; rate ratio, 0.83).

There was no difference between groups in the risk of death, but the study lasted only a year and was not powered for that endpoint, Dr. Wedzicha pointed out. "We are seeing less deaths in patients generally in COPD because we are monitoring them very carefully." Indacaterol-glycopyrronium was also superior to salmeterol-fluticasone based on scores on the St. George's Respiratory Questionnaire, use of rescue medication, and lung function.

The indacaterol-glycopyrronium formulation available in the United States, which contains lower doses of the drugs and is used twice-daily, would likely net results similar to those seen in the trial, she speculated. However, once-daily treatment is generally associated with better compliance.

The inflammatory component of COPD still needs attention, according to Dr. Wedzicha. "There is no good evidence that a LABA-LAMA is doing anything to the underlying airway inflammation ... I think a major unmet need now is novel anti-inflammatory agents," she said.

Dr. Wedzicha disclosed that she received nonfinancial support from Novartis during the study, as well as grant support and personal fees from various drug companies. The trial was sponsored by Novartis.

VIEW ON THE NEWS

Dr. Vera A. De Palo, MBA, FCCP, comments: As a disease, COPD has a significant impact on quality of life for our patients. Frequent returns to the hospital have many of us focusing on the care and support that our patients receive. As we redesign the experience of care for our patients with COPD, this trial demonstrates that we may have another useful tool in the therapeutic armamentarium which may be of benefit to COPD patients. Improving quality of life for these patients will lessen the burden of this chronic disease.

Nighttime extubations linked to poorer outcomes

BY SUSAN LONDON
Frontline Medical News

SAN FRANCISCO – Mechanically ventilated patients in the intensive care unit (ICU) have poorer outcomes if extubated during the night instead of during the day, based on a retrospective cohort study reported at an international conference of the American Thoracic Society.

Overall, 20% of the nearly 98,000 adult patients studied were extubated during nighttime hours, between 7:00 p.m. and 7:00 a.m., according to data presented in a session and a related press conference.

Compared with patients extubated during daytime hours, patients extubated during nighttime hours had higher rates of ICU and hospital death, with the absolute difference ranging from 1% to 5%. Additionally, among those mechanically ventilated for at least 12 hours, nighttime extubation was associated with an absolute 2% increase in the risk of reintubation.

FRONTLINE MEDICAL NEWS

Patients extubated at night had higher rates of ICU and hospital death, with the absolute difference ranging from 1% to 5%, Dr. Gershengorn said.

"I think this is the first large-scale study that looks at a practice that, although not as common as we thought it was, is still done about a fifth of the time and even with decreasing rates, is not a rare practice on our units," commented lead author Dr. Hayley B. Gershengorn of the department of medicine (critical care) and the Saul R. Korey department of neurology at the Albert Einstein College of Medicine, New York.

"As we have increasing staffing [overnight] and maybe an increasing push to move people through our ICUs, we need to probably take some care because although we can't demonstrate a causal link, it is quite concerning, this consistent finding of increased mortality and reintubation in these folks," she said.

There are several possible reasons for the observed heightened risks of death and reintubation with nighttime extubation that could not be fully explored in the study, Dr. Gershengorn said.

"We were not able to identify the indication for extubation or discontinuation of mechanical ventilation. So one of the concerns that we have is that it's probably more common that folks unintentionally extubate themselves or someone unintentionally extubates them overnight, when staffing is less," she explained. "The other part, which we tried to adjust for but we don't have perfect data on, is what is the staffing overnight," including factors such as the ratio of nurses to patients and how many units an intensivist is covering, not just whether he or she is present.

"In terms of the reintubation risk being higher in the [group with longer duration of mechanical ventilation], the question I have is whether or not there is less comfort with somebody looking less well when there is less staff around, and whether or not there may be a quicker trigger to reintubate them if they don't look so great," she said.

The majority of intubated patients are unlikely to improve enough physiologically to prompt nighttime extubation rather than waiting until daytime, according to Dr. Gershengorn. But there are at least two groups whom clinicians might want to extubate at night.

One group is those who underwent elective surgery during the day. "They are waiting to come out of anesthesia, and the plan is to discontinue mechanical ventilation at the time that that occurs," she explained. Another group is those who are agitated on the ventilator, require more sedation than usual, and suddenly awake at night. "These patients are really hard to keep comfortable. I can [sedate them] again and try this problem all over again tomorrow morning, or I can just bite the bullet and pull the tube out," she said.

The investigators analyzed data from the Project IMPACT critical care medicine database, in which data are prospectively collected for benchmarking purposes. In all, they studied 97,844 mechanically ventilated adults from 165 medical and surgical ICUs across the United States between 2000 and 2009.

Results showed that nighttime extubation was more common among elective surgical patients, those coming from the operating room or a postanesthesia care unit, and those mechanically ventilated for less than 12 hours.

In a finding that Dr. Gershengorn described as surprising, there was a temporal trend by which the adjusted proportion of extubations performed at night actually decreased in more recent years during the study period.

The investigators next looked at outcomes among 10,279 propensity-matched pairs of patients, one member of the pair having been extubated during the night and the other having been extubated during the day.

Among those mechanically ventilated for less than 12 hours, nighttime extubation was associated with higher ICU mortality (5.6% vs. 4.6%; $P = .025$) and hospital mortality (8.3% vs. 7.0%; $P = .014$). Findings were inconsistent for length of stay, with nighttime extubation associated with a shorter ICU stay but a longer hospital stay.

Among patients mechanically ventilated for 12 hours or longer, those extubated during the night had a higher rate of reintubation (14.6% vs. 12.4%; *P* less than .001), as well as higher ICU mortality (11.2% vs. 6.1%; *P* less than .001) and hospital mortality (16.0% vs. 11.1%; *P* less than .001). Lengths of stay did not differ by extubation time of day in this group.

In sensitivity analyses, findings were similar when the definition of nighttime extubation was altered to the hours of midnight to 5 a.m. and when analyses were restricted to nonpalliative patients, according to Dr. Gershengorn.

The lead author disclosed that she had no relevant conflicts of interest.

VIEW ON THE NEWS

Dr. Steven Q. Simpson, FCCP, comments: This is an interesting study, but we are left without some important information. What extubation criteria were met for any/all patients, regardless of the time of day of extubation? What type of nocturnal physician staffing was available? Were extubation protocols used, or was the extubation decision made by a bedside physician? One would like to see additional information before concluding that nocturnal extubation is definitely hazardous.

Nonbenzodiazepines reduced time to extubation

BY BRIAN HOYLE
Frontline Medical News

FROM CHEST

The nonbenzodiazepines propofol and dexmedetomidine reduce the time to extubation, compared with benzodiazepines, suggest results of an observational study published in Chest.

"This study found that sedatives vary in their associations with [ventilator-associated events] and time to extubation but not in their associations with time to hospital discharge or mortality. Both propofol and dexmedetomidine were associated with less time to extubation, compared with benzodiazepines," wrote Dr. Michael Klompas of the department of population medicine at Harvard Medical School and Harvard Pilgrim Health Care Institute, both in Boston, and colleagues (Chest. 2016 Jun;149[6]:1373-9).

Current sedation guidelines for mechanical ventilation recommend using nonbenzodiazepines to lightly sedate patients, whenever possible.

Compared with the use of benzodiazepines, the uses of propofol and dexmedetomidine were associated with shorter times to extubation with hazard ratios of propofol vs. benzodiazepines and dexmedetomidine vs. benzodiazepines of 1.4 (*P* less than .0001) and 2.3 (*P* less than .0001), respectively. In the relatively few cases involving uses of dexmedetomidine that were available, this sedative was also associated with shorter time to extubation, compared with propofol (HR, 1.7; *P* less than .0001).

Uses of benzodiazepines and

Continued on following page

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propofol were associated with increased risk for ventilator-associated events (VAEs), compared with regimens not involving them; for benzodiazepine use, the HR was 1.4 ($P = .002$) and for propofol, the HR was 1.3 ($P = .003$). Dexmedetomidine use, in contrast, was not associated with increased risk for VAEs ($P = .92$).

Regarding hazards for hospital discharges and hospital deaths, using each sedative or sedative class studied had similar outcomes.

Both propofol and dexmedetomidine were associated with less time to extubation, compared with benzodiazepines.

The observational study involved 9,603 retrospectively identified mechanical ventilations.

All consecutively occurring invasive mechanical ventilations lasting 3 days or longer in Boston's Brigham and Women's Hospital between July 1, 2006 and December 31, 2013 were studied.

The researchers evaluated the impact that daily use of propofol, dexmedetomidine, and benzodiazepines have on VAEs, time to extubation, time to hospital discharge, and death in a large cohort of patients.

This study's findings were similar to those of prior randomized controlled trials, especially concerning the time to extubation, the researchers said. "The large number of episodes of mechanical ventilation in our trial dataset, however, allowed us to extend conceivable but underpowered signals from randomized controlled trials."

A limitation of this study is that it was a single-center retrospective analysis, which may have caused some of its findings to be attributable to "residual confounding and/or idiosyncratic local practice patterns."

Other limitations include the lack of measurements of patients' total doses or adjusted doses per kilogram of body weight, a possible overtraining of the analysis model used to adjust for severity of illness, and a relatively low number of patients treated with dexmedetomidine, with most of such patients undergoing cardiac surgery.

Funding was provided by the Centers for Disease Control and Prevention.

Dr. Klompas and the other researchers had no disclosures.

VIEW ON THE NEWS

Dr. Vera A. De Palo, MBA, FCCP, comments: As physicians and other health-care prescribers, we must remember that the pharmacokinetics of the medications that we prescribe are important to keep in mind as we are selecting those medications to achieve certain effects (in the study cited, sedation) in the process of care delivery. Careful consideration of the patient's physiology, pathophysiology, and therapeutic goals, along with an understanding of the pharmacokinetics of the medications we chose, should guide our medication selection practices.

Midodrine cuts ICU days in septic shock patients

BY HEIDI SPLETE
Frontline Medical News

FROM CHEST

Septic shock patients who received midodrine needed significantly fewer intravenous vasopressors during recovery and had shorter hospital stays, based on data from a retrospective study of 275 adults at a single tertiary care center.

In many institutions, policy dictates that patients must remain in the ICU as long as they need intravenous vasopressors, wrote Dr. Micah R. Whitson of North Shore-LIJ Health System in New Hyde Park, N.Y., and colleagues. "One solution to this problem may be replacement of IV vasopressors with an oral agent."

"Midodrine facilitated earlier patient transfer from the ICU and more efficient allocation of ICU resources," the researchers wrote (Chest. 2016;149[6]:1380-83).

The researchers compared data on 135 patients treated with midodrine in addition to an intravenous vasopressor and 140 patients treated with an intravenous vasopressor alone.

Overall, patients given midodrine received intravenous vasopressors for 2.9 days while the other group received intravenous vasopressors for 3.8 days, a significant 24% difference. Hospital length of stay was not significantly different, averaging 22 days in the midodrine group and 24 days in the intravenous vasopressor–only group. However, ICU length of stay averaged 7.5 days in the midodrine group and 9.4 days in the vasopressor-only group, a significant 20% reduction. Further, the midodrine group was significantly less likely to reinstitute intravenous vasopressors than the intravenous vasopressor–only group (5.2% vs. 15%, respectively). ICU and hospital mortality rates were not significantly different between the two groups, Dr. Whitson and associates reported.

Patients in the midodrine group received a starting dose of 10 mg every 8 hours, which was increased incrementally until they no longer needed intravenous vasopressors. The maximum midodrine dose in the study was 18.7 mg every 8 hours, and the average duration of use was 6 days.

The patients' average age was 65 years in the intravenous vasopressor group and 69 years in the midodrine group. Other demographic factors did not significantly differ between the two groups.

One patient discontinued midodrine before discontinuing an intravenous vasopressor because of bradycardia, which resolved without additional treatment.

The findings were limited by the observational nature of the study and the use of data from a single center, the investigators noted. The results, however, support the safety of midodrine and the study "lays the groundwork for a prospective, randomized controlled trial that will examine efficacy, starting dose, escalation, tapering and appropriate patient selection for midodrine use during recovery from septic shock," they said.

The researchers had no financial conflicts to disclose.

Renal replacement delay may benefit critically ill

BY SUSAN LONDON
Frontline Medical News

SAN FRANCISCO – Delaying renal replacement therapy in critically ill patients with severe acute kidney injury appears to be not only safe but beneficial, based on a randomized controlled trial conducted in France.

The trial, Artificial Kidney Initiation in Kidney Injury (AKIKI), was conducted among 620 adult patients from 31 intensive care units and was led by Dr. Stéphane Gaudry of Assistance Publique–Hôpitaux de Paris.

The death rate did not differ for groups assigned to an early versus a late initiation strategy, according to results presented at an international conference of the American Thoracic Society and simultaneously published (N Engl J Med. 2016 May 15. doi: 10.1056/NEJMoa1603017).

Moreover, nearly half of the patients in the delayed initiation group were able to avoid renal replacement therapy. And they were less likely to develop bloodstream infections and had more rapid onset of diuresis (heralding recovery of renal function) than did peers in whom the therapy was initiated early.

"Our study should not be interpreted as suggesting that a 'wait and see' approach is safe for all patients. Indeed, careful surveillance is mandatory when deciding to delay renal-replacement therapy in patients with severe acute kidney injury so that any complications will be detected and renal-replacement therapy initiated without delay," the researchers said.

Further, the "findings may not be generalizable, because more than 50% of the patients in our trial received intermittent hemodialysis as the first method of therapy and only 30% of the patients received continuous renal-replacement therapy as the sole method (with no intermittent dialysis at any time)."

The author of an accompanying editorial, Dr. Ravindra L. Mehta of the University of California, San Diego, lists some caveats in interpreting the trial's findings as support for the delayed initiation strategy.

For example, he notes, the longer time to initiation with the delayed strategy contributed to worsening of metabolic and clinical status in the patients who ultimately did need therapy; the study did not assess the development of chronic kidney disease; and the types of renal replacement therapy selected for patients seem "surprising" as the majority put on this therapy needed vasopressors.

"Our study should not be interpreted as suggesting that a 'wait and see' approach is safe for all patients ... careful surveillance is mandatory when deciding to delay renal-replacement therapy," said Dr. Gaudry and colleagues.

"The findings highlight a need for dynamic risk-stratification tools to identify patients who will not need renal-replacement therapy for management of their acute kidney injury," Dr. Mehta concluded, noting that ongoing studies should help inform management in this area. "Meanwhile, we should focus on the timely application of renal-replacement therapy while considering individual patient characteristics, process-of-care elements, and logistics to achieve therapeutic goals …"

Patients were eligible for the trial if they had severe acute kidney injury, defined as Kidney Disease: Improving Global Outcomes (KDIGO) stage 3; required mechanical ventilation, catecholamine infusion, or both; and did not have a potentially life-threatening complication related to renal failure.

In those assigned to the early strategy, renal replacement therapy was started immediately after randomization. In those assigned to the delayed strategy, it was started if any of several criteria was met: severe hyperkalemia, metabolic acidosis, pulmonary edema, blood urea nitrogen level higher than 112 mg/dL, or oliguria for more than 72 hours after randomization. The specific type of renal replacement therapy was left up to each study site.

The median time between randomization and initiation of renal replacement therapy was 2 hours in the early strategy group and 57 hours in the delayed strategy group.

The estimated 60-day mortality rate – the primary outcome – was 48.5% with early initiation of therapy and 49.7% with delayed initiation, a nonsignificant difference. Fully 49% of the delayed strategy group never received renal replacement therapy. Also, patients in this group were half as likely as were peers in the early initiation group to develop a bloodstream infection (5% vs. 10%), and they had more rapid onset of diuresis (*P* less than .001).

The groups were essentially the same with respect to the rate of gastrointestinal bleeding and the lengths of stay in the intensive care unit and in the hospital.

Dr. Gaudry disclosed that he received grant support from the French Ministry of Health during the study, and from XENIOS France outside the research. The trial was supported by a grant from Programme Hospitalier de Recherche Clinique National, 2012 (AOM12456), funded by the French Ministry of Health.

Hospital-acquired RVIs drive up in-hospital death rate

BY KARI OAKES
Frontline Medical News

BOSTON – Hospital-acquired respiratory viral infections may be a significant and underappreciated cause of morbidity and mortality among hospitalized patients.

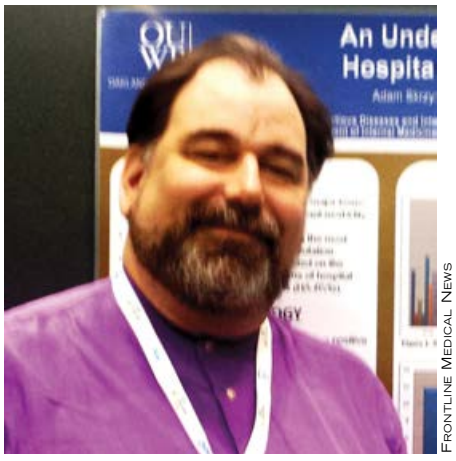
According to a multisite, retrospective chart review of 44 patients with hospital-acquired respiratory viral illnesses (HA-RVIs), 17 patients (39%) died in-hospital. Further, of the 27 who survived, 18 (66.6%) were discharged to an advanced care setting rather than to home, though just 11/44 (25%) had been living in an advanced care setting before admission.

For hospitalizations complicated by HA-RVI, the average length of stay was 30.4 days, with a positive respiratory virus panel (RVP) result at a mean 18 days after admission.

"HA-RVIs are an underappreciated event and appear to target the sickest patients in the hospital," said coauthor Dr. Matthew Sims, director of infectious diseases research at Beaumont Hospital, Rochester, Mich., at a poster session of the annual meeting of the American Society of Microbiology.

First author Dr. Adam K. Skrzynski, also of Beaumont Health, and his coauthors performed the analysis of 4,065 patients with a positive RVP result during hospitalization at a regional hospital system in the September 2011-May 2015 study period; the 1.1% of patients with positive results who formed the study cohort had to have symptoms of a respiratory infection occurring after more than 5 days of hospitalization. Mortality data were collected for the first 33 days of hospitalization.

Positive RVP results for those included in the study came primarily from nasopharyngeal swab (n = 32), with the remainder from bronchoalveolar lavage (n = 11) and sputum (n = 1). Most patients were female (29/44, 66%), and elderly, with an average age of 74 years. In an interview, Dr. Sims said that many patients were smokers, and that chronic obstructive pulmonary disease and obesity were common comorbidities.



FRONTLINE MEDICAL NEWS

HA-RVIs target the sickest patients, Dr. Matthew Sims said.

The prognosis was particularly grim for the 12 patients who were admitted to the ICU: 10 died after an average 9.6 days in the ICU. "Intubation didn't help these patients," said Dr. Sims. Nine patients were intubated within 7 days of their positive RVP results. Intubation lasted an average 7.6 days, and all nine of patients died.

The RVP came into use in 2011 and made it possible to identify if a respiratory virus was causing symptoms – and which virus was the culprit – said Dr. Sims. For the studied population, 13 of 44 patients had influenza; 11 of those had influenza A and 2 had influenza B. There were10 positive RVP results for parainfluenza.

Dr. Skrzynski reported no outside funding source, and the study authors had no financial disclosures.

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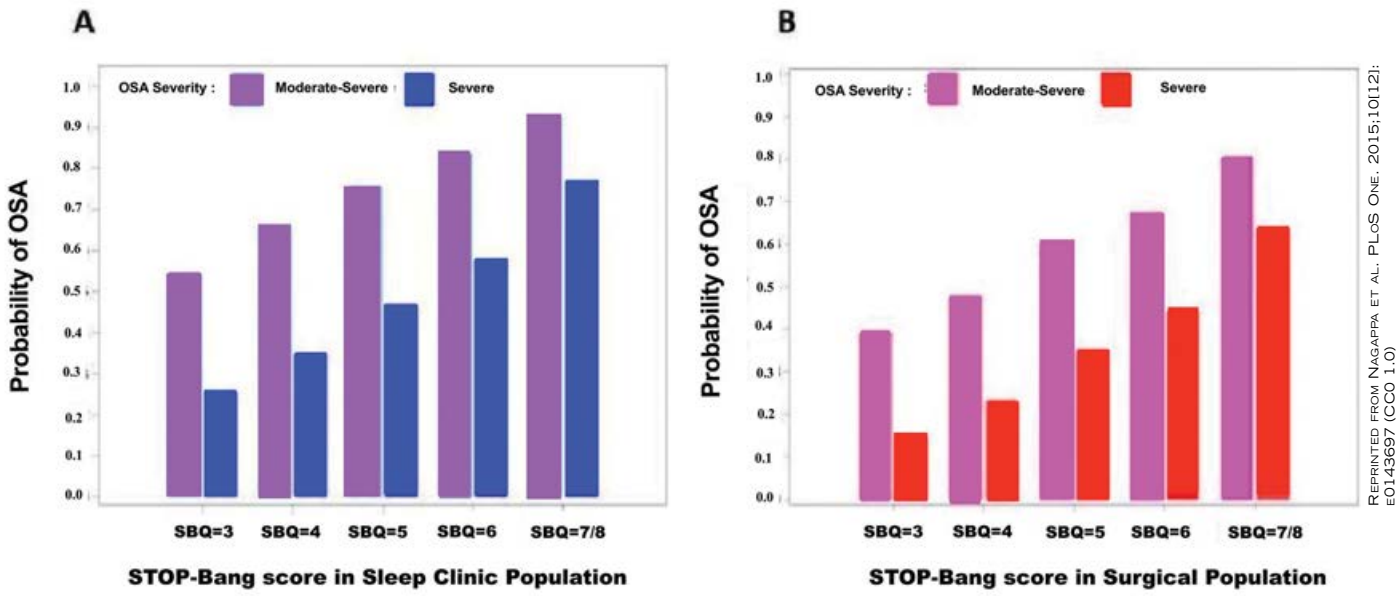
SLEEP STRATEGIES: The flexibility of the STOP-Bang Questionnaire to screen for OSA: A practical approach

BY DR. MAHESH NAGAPPA AND DR. FRANCES CHUNG



Obstructive sleep apnea (OSA) is a potentially serious sleep disorder in which breathing repeatedly stops and starts during sleep. OSA occurs when the throat muscles intermittently relax and block the airway during sleep. The condition is usually associated with several other chronic medical conditions leading to poor quality of life.

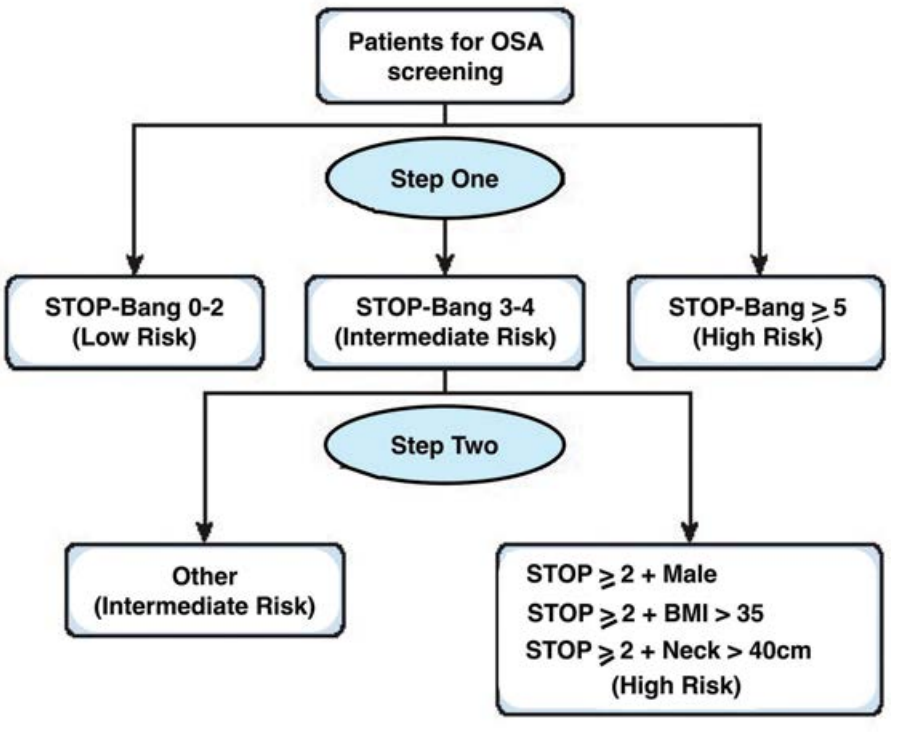
It is estimated that at least 25 million adults are affected by OSA in the United States. Further, the obesity epidemic has increased the prevalence of OSA in the last 2 decades. The prevalence of OSA can be higher in patients undergoing surgery. For example, 70% of the patients undergoing bariatric surgery have OSA, whereas 48% of patients undergoing cardiac surgery have moderate-severe OSA. Alarmingly, in 80% of patients with moderate-severe OSA, the disorder remains undiagnosed and untreated, threatening public health and safety.

Patients with OSA can experience multiple complications when receiving sedatives and opioids during anesthesia (Opperer. *Anesthesia Analgesia*. 122[5]:1321). These drugs may diminish the protective arousal reflex triggered by bouts of hypoxia, thereby increasing the risk of prolonged periods of apnea and possibly respiratory arrest.

Sedatives and narcotics can decrease pharyngeal muscle tone, which can worsen the existing OSA and increase upper airway resistance. Undiagnosed and untreated OSA may be a contributing factor in many of these complications. Effective screening/diagnosis and treatment of OSA are considered to be important steps to reduce health-care spending, improve chronic disease management, and reduce complications.

The STOP-Bang Questionnaire

The gold standard for the diagnosis of OSA is overnight polysomnography. However, it is time consuming, labor intensive, and costly. The STOP-Bang Questionnaire is considered to be the most validated screening tool for OSA for various populations (Nagappa et al. *PLoS One*. 2015;10[12]:e0143697).



The STOP-Bang Questionnaire includes four questions used in the STOP Questionnaire plus four additional demographic queries, a total of eight dichotomous (yes/no) questions related to the clinical features of sleep apnea (**S**noring, **T**iredness, **O**bserved apnea, high blood **P**ressure, **B**MI, **a**ge, **n**eck circumference, and male **g**ender). For each question, answering "yes" scores 1, a "no" response scores 0, and the total score ranges from 0 to 8 (see www.stopbang.ca).

The Questionnaire can be completed quickly and easily (usually within 1-2 minutes), and the overall response rates are typically high (90%-100%). Because of its ease of use, efficiency, and high sensitivity, the STOP-Bang Questionnaire has been widely adopted in various populations, such as sleep clinics and the surgical and general population.

The STOP-Bang Questionnaire has demonstrated a high sensitivity using a cutoff score of greater than or equal to 3: 84% in detecting any sleep apnea (apnea-hypopnea index greater than 5 events/h), 93% in detecting moderate to severe sleep apnea (AHI greater than 15 events/h), and almost 100% in detecting severe sleep apnea (AHI greater than 30 events/h). The corresponding specificities were 56.4%, 43%, and 37% (Chung et al. *Anesthesiology*. 2008;108[5]:812). If patients score 0-2 on the STOP-Bang Questionnaire, they are considered to be at low risk of OSA, and the possibility of moderate to severe sleep apnea can be ruled out.

The modest specificity of the STOP-Bang Questionnaire may yield moderately high false-positive cases. This may lead to unwanted sleep study referrals and increased health care expenditure.

There are several ways by which the specificity can be improved, thereby decreasing false-positive rates.

Setting a threshold for the STOP-Bang scores in different population

The main advantage of the STOP-Bang scores is its flexibility to use different scores for different populations. For example, in a bariatric population, a STOP-Bang score of greater than or equal to 4 can be used. On the other hand, in an ENT population, where we would like to identify a majority of patients with moderate-severe OSA, a STOP-Bang score of greater than or equal to 5 can be used.

In the sleep clinic population, as the STOP-Bang score cut-off increased from 3 to 8, the specificity increased from 52% to 100%, and the PPV increased continuously from 93% to 100% for any OSA (AHI greater than or equal to 5). A similar pattern was seen in the surgical population, as the STOP-Bang score cutoff increased from 3 to greater than or equal to 7, the specificity increased from 40% to 98%, and the PPV increased from 75% to 82% for any OSA (AHI greater than or equal to 5) (Nagappa et al. *PLoS One*. 2015;10[12]:e0143697).

Regional practices should decide the appropriate threshold of screening tests, after considering the implications for missed diagnoses and cost of care. There is a trade-off between sensitivity and specificity.

Continued on page 19

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- If a patient exceeds the maximum monthly benefit of $2,500, the patient will be responsible for the outstanding balance.
- Patients, pharmacists, and prescribers cannot seek reimbursement from health insurance or any third party, for any part of the benefit received by the patient through this offer.
- Your acceptance of this offer confirms that this offer is consistent with your insurance and that you will report the value received as may be required by your insurance provider.
- Only valid in the United States or Puerto Rico; this offer is void where restricted or prohibited by law.
- No membership fees.
- The ZYFLO Connect program is not insurance.
- The ZYFLO Connect program cannot be combined with any other rebate/coupon, free trial, or similar offer for the specified prescription.
- The ZYFLO Connect program expires on December 31, 2016.
- The ZYFLO Connect program is limited to one per person.
- Chiesi USA reserves the right to rescind, revoke, or amend this offer at any time without notice.
- **The ZYFLO Connect program is only offered through distribution from Foundation Care, a full-service pharmacy serving patients in all 50 states and Puerto Rico.**

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Chiesi

ZYFLO CR®

(zileuton) extended-release tablets

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At lower thresholds, there is improved sensitivity with potentially increased resource utilization, whereas increasing the threshold will result in loss of sensitivity and increased false-negative rates but improved resource utilization. A higher threshold should be adopted in the population with a lower prevalence of OSA.

STOP-Bang score and probability of OSA

In both sleep clinic patients (Fig 1; Panel A) and surgical patients (Fig 1; Panel B), the probability of moderate-to-severe OSA or severe OSA increased as the STOP-Bang score increased from 3 to 7/8. With higher scores, there is a more profound increase in the probability of severe OSA, compared with moderate OSA (Chung et al. *Br J Anaesth*. 2012;108[5]:768).

Alternative models for scoring the STOP-Bang Questionnaire

The individual items on the Questionnaire do not share an equal predictive weight for OSA. In the "Bang" components, body mass index greater than 35 kg/m^2, neck circumference greater than 40 cm, and male gender are more predictive than age greater than 50 years.

The predictive performance of the specific combinations of items has been explored. Compared with the specificity of 31% for detecting moderate to severe OSA, specific combinations significantly improve the specificity to detect any OSA (AHI greater than 5), moderate to severe OSA (AHI greater than 15), and severe OSA (AHI greater than 30) at the expense of sensitivity.

The specificity to detect moderate to severe OSA increases to 85% for a STOP score greater than or equal to 2 + BMI greater than 35 kg/m^2; to 79% for a STOP score greater than or equal to 2 + neck circumference > greater than 40 cm (16 in); and to 77% for a STOP score greater than or equal to 2 + male, respectively.

These combinations can assist in accurately identifying more patients with moderate to severe OSA (Chung et al. *J Clin Sleep Med*. 2014;10[9]:951).

The STOP-Bang Questionnaire and serum bicarbonate

Serum bicarbonate (HCO_3–) is significantly correlated to AHI, and the addition of serum HCO_3– greater than or equal to 28 mmol/L to a STOP-Bang score greater than or equal to 3 improves the specificity to predict moderate-severe OSA but decreases its sensitivity (Chung et al. *Chest*. 2013;143[5]:1284).

For a STOP-Bang score of greater than or equal to 3 + HCO_3– greater than or equal to 28 mmol/L), the specificity for detecting moderate to severe OSA increases from 30% to 82%, and from 28% to 80% for detecting severe OSA, respectively.

A two-step strategy for using STOP-Bang Questionnaire

A two-step algorithm using the STOP-Bang Questionnaire identifies patients effectively with a high probability of moderate to severe sleep apnea (Fig 2) (Chung et al. *Chest*. 2016;149[3]:631).

The first step is to check the STOP-Bang score. If a patient scores 0-2 on the STOP-Bang Questionnaire, he or she is unlikely to have moderate to severe OSA. Conversely, a patient with a STOP-Bang score of 5-8 has a high probability of moderate to severe OSA.

The second step is for the patients

Continued on following page

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with STOP-Bang scores of 3 or 4.

These patients can be further classified as having a higher risk for moderate to severe OSA if one of the following conditions is met: (1) a STOP score greater than or equal to 2 + BMI greater than 35 kg/m^2; (2) a STOP score that is greater than or equal to 2 + male gender; (3) a STOP score that is greater than or equal to 2 + neck circumference greater than 40 cm (16 in); or (4) a STOP-Bang score greater than or equal to 3 + serum HCO_3– greater than or equal to 28 mmol/L.

The STOP-Bang Questionnaire and perioperative complications

The STOP-Bang Questionnaire not only identifies the high-risk patients with OSA but also may have a strong association toward predicting perioperative complications (Vasu et al. *Arch Otolaryngol Head Neck Surg.* 2010;136[10]:1020).

The important step of screening patients with OSA using the STOP-Bang Questionnairmay create an awareness among the perioperative team resulting in decreased complications (Veenstra et al. *Crit Care Nurs Clin N Am.* 2014;26[4]:499).

The Joint Commission's Division of Healthcare Improvement has

raised strong concerns regarding the lack of training for health-care professionals to recognize OSA. A guideline published by the Society of Anesthesia and Sleep Medicine recommends using a screening tool to identify high-risk patients with OSA (Chung et al. *Anesthesia Analgesia.* 2016;June 1: Epub ahead of print).

There is preliminary evidence that patients who have diagnosed OSA and a CPAP prescription had significantly reduced postoperative cardiovascular complications (cardiac arrest and shock) by more than 50% vs patients with undiagnosed OSA (Mutter et al. *Anesthesiology.* 2014;121[4]:707).

Conclusion

The STOP-Bang Questionnaire is a simple, practical, and flexible screening tool that is used to identify the high-risk OSA patient.

More information is available at www.stopbang.ca.

Dr. Chung is with the department of anesthesia, Toronto Western Hospital – University Health Network, University of Toronto, ON, Canada.
Dr. Nagappa is with the department of anesthesia & perioperative medicine, London Health Sciences Centre and St. Joseph Health Care London, Western University, London, ON, Canada.

USPSTF draft rec opposes asymptomatic screening

BY KATIE WAGNER LENNON
Frontline Medical News

The U.S. Preventive Services Task Force has issued a draft recommendation opposing screening for obstructive sleep apnea (OSA) in adults who are asymptomatic for the breathing disorder.

The USPSTF's opposition is based on its determination that there is insufficient evidence to assess the balance of benefits and harms of screening for OSA in asymptomatic adults in primary care settings, giving the service an "I" grade. The recommendation and a draft evidence review are available for public comment until July 11 at 8:00 p.m. EST.

The draft recommendation is the first that the USPSTF has ever made about sleep apnea, according to the draft evidence review. The recommendation "applies to asymptomatic

adults (aged 18 years and older) and adults with unrecognized symptoms of OSA." It does not apply to children, adolescents, pregnant women, persons presenting with symptoms of or concerns about OSA, those who are being referred for evaluation or treatment of suspected OSA, and those who have acute conditions that could trigger the onset of OSA.

The draft recommendation "applies to asymptomatic adults (aged 18 years and older) and adults with unrecognized symptoms of OSA."

"Reported estimates of OSA prevalence vary due to differing definitions of OSA, sampling bias, and year of study publication. A 2013 systematic review reported an estimated prevalence of 2%-14% based on four community-based studies, while two U.S.-based studies conducted in the 1990s reported an estimated prevalence of 10% for mild OSA and 3.8%-6.5% for moderate or severe OSA," according to the recommendation.

The USPSTF was unable to find adequate evidence on the direct harms or the benefits of screening for OSA in asymptomatic populations, including their magnitude.

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Most primary care clinicians do not routinely screen for OSA, according to the recommendation. While the Epworth Sleepiness Scale, STOP Questionnaire, STOPBang Questionnaire, Berlin Questionnaire, and Wisconsin Sleep Questionnaire are potential screening tests for OSA, none of these questionnaires has been validated in a primary care setting.

"There is uncertainty about the clinical utility of all potential screening tools," and the USPSTF found no studies that prospectively evaluated screening questionnaires or clinical prediction tools to report calibration or clinical utility for improving health outcomes," the draft evidence review said.

The USPSTF also found no studies evaluating the effect of screening for OSA on health outcomes or that directly evaluated benefits or harms of screening for OSA.

The recommendation calls for further research on the health outcomes of screening for OSA in asymptomatic persons and the role of sleepiness in determining health outcomes.

The following are needed:

- The identification of valid and reliable clinical prediction tools that could accurately determine which asymptomatic persons (or persons with unrecognized symptoms) would benefit from further evaluation and testing for OSA.

"There is uncertainty about the clinical utility of all potential screening tools," and the USPSTF found no studies that prospectively evaluated screening questionnaires.

- Studies that evaluate the effect of OSA treatments or interventions on health outcomes that are adequately powered and have an appropriate length of follow-up.
- Studies that evaluate whether improvement in the apnea-hypopnea index leads to improvement in health outcomes.
- More data on the natural history of mild sleep apnea.

The final evidence review will be used to inform the final USPSTF recommendation statement, which is expected to be issued later this year.

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VIEW ON THE NEWS

Dr. David A. Schulman, FCCP, comments: The draft statement from the Preventive Services Task Force recommending against screening asymptomatic patients with standardized OSA questionnaires warrants a careful read. Many sleepy patients may not complain of their fatigue unless specifically asked, choosing to attribute their symptoms to inactivity, age, weight or a lack of exercise instead of a potential underlying sleep disorder. Assessment of patients' sleep habits and patterns by primary care physicians remains a critical component of preventive health to improve identification of the twenty-plus million Americans with sleep-disordered breathing.

Lung tests limited for predicting post op outcomes

BY MARK S. LESNEY
Frontline Medical News

Routine preoperative pulmonary function tests appear to have only limited utility in predicting outcomes in patients undergoing cardiothoracic surgery when the Society of Thoracic Surgeons risk score is available, according to the results of a retrospective study.

Dr. Alexander Ivanov of New York Methodist Hospital, Brooklyn, and his colleagues conducted a database analysis of 1,685 patients undergoing index cardiac surgery at New York Methodist Hospital between April 2004 and January 2014. They used the STS risk model version 2.73 to estimate postoperative risk of respiratory failure (defined as the need for mechanical ventilation greater than or equal to 72 hours, or reintubation), prolonged postoperative length of stay (defined as greater than 14 days), and 30-day all cause mortality in these patients, according to their report in The Journal of Thoracic and Cardiovascular Surgery (2016;151:1183-9).

They plotted the receiver operating characteristics curve for the STS score for each of these adverse events and compared the resulting area under the curve (AUC) with the AUC after adding pulmonary function testing parameters and COPD classifications.

A total of 1,412 patients had a calculated STS score, of which 751 underwent pulmonary function testing (53%).

In general, patients who had pulmonary function testing were older and had higher rates of comorbidities and more complex cardiothoracic surgery compared with their counterparts, according to Dr. Ivanov. These patients also had significantly elevated STS risk for prolonged ventilation (12.4% vs. 10.3%), prolonged postoperative length of stay (8.9% vs. 7.2%), and 30-day mortality (2.7% vs. 2.2%).

The decision to perform pulmonary testing was left to the treating physician. Of those patients tested, 652 had bedside spirometry and 99 had formal laboratory testing. Forced expiratory volume in 1 second (FEV_1) and forced volume vital capacity (FVC) values were determined by taking the best of three trials. COPD was diagnosed in cases of an FEV_1/FVC ratio of less than 70%.

Among these patients, 4.5% developed postoperative respiratory failure, and there was no statistically significant difference in the respiratory failure rate between patients with and without pulmonary function testing. In addition, there was no significant difference in 30-day mortality between these patients (1.9% vs. 2.1%). However, a total of 6.9% had a prolonged postoperative length of stay, with a significantly higher rate in the patients with pulmonary function testing than without (8.8% vs. 4.7%).

Dr. Ivanov and his colleagues found that the AUC of the STS score was 0.65 (95% confidence interval [CI], 0.55-0.74)for respiratory failure, 0.67 (95% CI, 0.6-0.74) for prolonged postoperative length of stay, and 0.74 (95% CI, 0.6-0.87) for 30-day mortality. Even though the STS score based upon clinical definitions of lung disease afforded only modest discriminatory ability for the three studied outcomes, they found that there was no significant added benefit to the predictive ability of these STS scores obtained by incorporating any of the pulmonary function testing parameters or COPD classifications studied.

"A possible physiological explanation for these findings may be that the examined pulmonary function testing variables do not depend solely on pulmonary parameters such as airway diameter, degree of obstruction, or lung elasticity, but rather on a patient's effort and muscle "strength," characteristics that are already well captured and accounted for in the current STS model," the researchers stated.

The authors had no disclosures.

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VIEW ON THE NEWS

Tests define lung function severity

Chronic lung disease is one of the risk factors included in the STS model for mortality, renal failure, prolonged ventilation, sternal wound infection, reoperation, and length of hospital stay. Mild, moderate, and severe CLD increases the odds ratio for those complications. A total of 20% of almost 1 million patients used in developing the current STS risk model had CLD.

The authors found that none of the pulmonary function testing parameters added to the predictive ability of the STS risk model for operative mortality, prolonged ventilation, or prolonged length of hospital stay. Because CLD is 1 of 40 preoperative and operative variables used in the STS risk model, an improvement in discrimination of only 1 of 40 variables is very unlikely to improve the overall model.

One may be tempted to conclude that it is not worth performing pulmonary function testing before cardiac surgery. However, remember once again the importance of precise and accurate data to support risk stratification. In science, behind each word resides a precise definition; without a pulmonary function test, we cannot define chronic lung disease severity.

Dr. Juan A. Crestanello is in the division of cardiac surgery, Wexner Medical Center, Ohio State University, Columbus. His remarks are from an invited commentary (J Thorac Cardiovasc Surg. 2016;151:1189-90).

Ex vivo lung perfusion may preserve lungs for more than 12 hours

BY RICHARD PIZZI
Frontline Medical News

BALTIMORE – The use of ex vivo lung perfusion (EVLP) may allow for the safe transplantation of lungs preserved for more than 12 hours, according to a study presented at the annual meeting of the American Association for Thoracic Surgery.

A research team at the University of Toronto evaluated the outcomes of transplant patients who received a lung with a preservation time of over 12 hours between January 2006 and April 2015 and compared them to the general lung transplant population.

Median hospital and ICU length of stay were similar between the two groups, and Kaplan-Meier survival curves between the two groups did not show any difference. Preservation time, donor PO2, and use of EVLP were not significant variables affecting survival.

FRONTLINE MEDICAL NEWS

To view our exclusive interview with Dr. Griffith, search for EVLP at www.chestphysician.org.

Dr. Bartley P. Griffith, chief of cardiac surgery at the University of Maryland, Baltimore, and a discussant on the paper at the meeting, said that the findings of the study open up the possibility of a more "planned" approach to transplantation.

"Anything that not only extends preservation time, but perhaps even improves quality of preservation, would be a godsend," Dr. Griffith said in a video interview.

He cautioned that the "devil is in the details," and that the data had to be examined closely. Nevertheless, Dr. Griffith said transplant surgeons should be grateful for the important work done by the University of Toronto team.

Dr. Griffith reported that he had no relevant financial disclosures.

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24-hour BREO—Approved for Asthma

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.**
- **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

- BREO is contraindicated for primary treatment of status asthmaticus or other acute episodes of chronic obstructive pulmonary disease (COPD) or asthma where intensive measures are required.
- BREO is contraindicated in patients with 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.
- 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.
- 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.

WARNINGS AND PRECAUTIONS (cont'd)

- 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 immediately 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.
- 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

- 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.

BREO ELLIPTA was developed in collaboration with Theravance

Reach for BREO

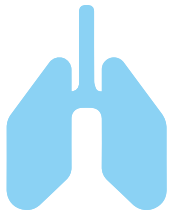
Reach With Confidence

In patients uncontrolled on an ICS alone, BREO has been proven to:

Deliver 24-hour lung function improvement

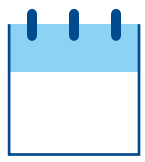
with one inhalation, once daily*

Reduce asthma exacerbations



in patients with a history of exacerbations†

Increase days <u>without</u> asthma symptoms



and increase days <u>without</u> use of rescue medication‡

Important Safety Information (cont'd)

DRUG INTERACTIONS (cont'd)

- 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 Brief Summary of Prescribing Information, including Boxed Warning, for BREO on the following pages.

Supporting Clinical Study Information

*In a randomized, double-blind (RDB) study of 1039 patients§ symptomatic on a mid- to high-dose ICS, BREO 100/25 once daily (n=312) demonstrated a 108 mL improvement from baseline in weighted mean (wm) FEV_1 (0-24 hours) at the end of the 12-week treatment period vs fluticasone furoate (FF) 100 mcg once daily (n=288) ($P<0.001$).[1] (In an RDB, placebo-controlled study of 609 patients§ symptomatic on a low- to mid-dose ICS, in a subset of patients, BREO 100/25 once daily [n=108] demonstrated a change from baseline in wm FEV_1 [0-24 hours] at the end of the 12-week treatment period vs FF 100 mcg once daily [n=106] of 116 mL [95% CI: –5, 236; $P=0.06$].[2])

†In a 24- to 76-week RDB study of 2019 patients§ with ≥1 exacerbations in the prior year, BREO 100/25 once daily (n=1009) reduced the risk of experiencing an exacerbation by 20% (Hazard Ratio=0.795, $P=0.036$) vs FF 100 mcg once daily (n=1010).[3] An exacerbation was defined as a deterioration of asthma requiring the use of systemic corticosteroids (SCS) for ≥3 days or an in-patient hospitalization or emergency department visit due to asthma that required SCS.

‡In an RDB study of 1039 patients§ symptomatic on a mid- to high-dose ICS, BREO 100/25 once daily (n=345) provided an increase from baseline in the % of rescue-free and the % of symptom-free 24-hour periods during the 12-week treatment period of 12.2% and 7.8%, respectively ($P\leq0.002$), vs FF 100 mcg once daily (n=346).[1]

§Studies included patients with asthma ≥12 years of age; BREO is only approved for use in patients ≥18 years of age.

References: 1. Bernstein DI et al. *J Asthma.* 2015. doi:10.3109/02770903.2015.1056350. **2.** Bleecker ER et al. *J Allergy Clin Immunol Pract.* 2014;2(5):553-561. **3.** Bateman ED et al. *Thorax.* 2014;69(4):312-319.

Visit BREOhcp.com for more information, including Patient Assistance Programs.

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 and is focused on the asthma indication. 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

1.2 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.
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. 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.
5.6 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, 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.
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)]*; 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.
6.2 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.

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 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 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.
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 was developed in collaboration with Theravance.

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Rotor ablation for atrial fibrillation strikes out

BY M. ALEXANDER OTTO
Frontline Medical News

SAN FRANCISCO – Focal impulse and rotor modulation-guided ablation for persistent atrial fibrillation – either alone or in conjunction with other procedures – increased procedural times without improving outcomes, according to the first randomized trial to assess its utility.

In fact, enrollment in the rotor ablation-only (RA) arm was halted early for futility.

"There was 100% recurrence" of atrial fibrillation, said senior investigator Dr. Andrea Natale, executive medical director of the Texas Cardiac Arrhythmia Institute, Austin.

There is no benefit to performing rotor ablation, at least with this mapping software.

DR. NATALE

"I'm surprised it took this long for a randomized study, because this system has been around for 5 or 6 years," noted Dr. Natale. "Our community should demand these sorts of studies earlier, because it's not fair for patients to go on with a procedure for years that has not been proven to be effective.

"For us, unless there is a new version of rotor mapping that I feel is significantly different, this will be the end of rotor ablation in my lab with the system we use," Dr. Natale said at the annual scientific sessions of the Heart Rhythm Society.

In the study, his team randomized 29 patients to RA only, 42 to RA plus pulmonary vein antral isolation (PVAI), and 42 to PVAI plus posterior wall and nonpulmonary vein trigger ablation.

At 1 year, four RA-only patients (14%), 22 RA plus PVAI patients (52%), and 32 patients in the PVAI plus trigger group (76%) were free of atrial fibrillation and atrial tachycardias without antiarrhythmic drugs ($P < .0001$).

Meanwhile, RA alone and RA plus PVAI cases took about 230 minutes, while the more effective PVAI plus trigger approach took about 130 minutes ($P < .001$).

There was "a very poor outcome

VIEW ON THE NEWS

Down, but not out

My gut sense is that there's something to rotor mapping, but we are not there yet. There are a lot of investment dollars and a lot of bright people working on this. It really is the Holy Grail to find the source of atrial fibrillation.

Dr. John Day is the director of Intermountain Heart Rhythm Specialists in Murray, Utah, and the current president of the Hearth Rhythm Society. He had no disclosures.

with rotor-only ablation," Dr. Natale said. "There isn't a benefit either alone or as an add-on strategy, at least with this mapping software."

Perhaps "people who think rotors don't exist are right," he added.

On the other hand, maybe the basket mapping catheter doesn't touch enough of the left atrium, or the software that makes sense of what the catheter detects needs to be improved, Dr. Natale noted.

All the patients were undergoing their first ablation. They were in their early 60s, on average, and most were men.

The mean left atrium diameter was about 47 mm, and mean left ventricle ejection fraction about 55%.

There were no statistically significant differences between the study arms.

Further, no significant differences were noted in outcomes between the 70% of patients with persistent atrial fibrillation and the 30% with long-standing persistent atrial fibrillation.

There was no industry funding for the work. Dr. Natale disclosed relationships with Biosense Webster, Boston Scientific, Janssen, Medtronic, and St. Jude Medical.

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Ultrasound bests auscultation for ETT positioning

BY DOUG BRUNK
Frontline Medical News

SAN DIEGO – Assessment of the trachea and pleura via point-of-care ultrasound is superior to auscultation in determining the exact location of the endotracheal tube, a randomized, single-center study found.

"It's been reported that about 20% of the time the endotracheal tube is malpositioned," study author Dr. Davinder S. Ramsingh said in an interview at the annual meeting of the American Society of Anesthesiologists. "Most of the time (the tube) is too deep, which can lead to severe complications."

In a double-blinded, randomized study, Dr. Ramsingh and his associates assessed the accuracy of auscultation vs. point-of-care ultrasound in verifying the correct position of the endotracheal tube (ETT). They enrolled 42 adults who required general anesthesia with ETT and randomized them to right main bronchus, left main bronchus, or tracheal intubation, followed by fiber optically–guided visualization to place the ETT. Next, an anesthesiologist blinded to the ETT exact location used auscultation to assess the location of the ETT, while another anesthesiologist blinded to the ETT exact location used point-of-care ultrasound to assess the location of the ETT. The ultrasound exam consisted of assessing tracheal dilation via standard cuff inflation with air and evaluation of pleural lung sliding, explained Dr. Ramsingh of the department of anesthesiology and perioperative care at the University of California, Irvine.


DR. RAMSINGH

Dr. Ramsingh reported that in differentiating tracheal versus bronchial intubations, auscultation demonstrated a sensitivity of 66% and a specificity of 59%, while ultrasound demonstrated a sensitivity of 93% and a specificity of 96%. Limitations of the study include that "we don't know the incidence of malpositioned endotracheal tubes in the operating room and that the patients were undergoing elective surgical procedures." The researchers reported having no financial disclosures.

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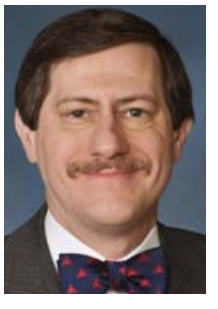
VIEW ON THE NEWS

Dr. Francis J. Podbielski, FCCP, comments:



Given the ubiquity of ultrasound in the operating room, generally employed to aid in placement of vascular catheters, this is a novel and very useful application of technology to ensure proper endotracheal tube placement.

IASLC proposes revising TNM classification

BY MARK S. LESNEY
Frontline Medical News

The International Association for the Study of Lung Cancer (IASLC) Staging and Prognostic Factors Committee has developed proposals for revision of the T, N, and M categories of the 8th edition of the TNM Classification for lung cancer due to be published in late 2016. The new classification will be enacted in January 2017.

The changes proposed were based on the results of an analysis of a new database of 94,708 cases donated from 35 sources in 16 countries around the world.

The methods used and the proposals made were published in the Journal of Thoracic Oncology (2016;11:39-51).

Candidate proposals for the TNM stage groups were developed in conjunction with proposed changes to the T and M categories, which were previously published (J Thorac Oncol 2015;10:990-1003, and 2015;10:1515-22). There were no proposed changes to the N.

Changes to some T and M descriptors will result in these cases being assigned to a different stage than that to which they would have been assigned in the 7th edition. In addition, some TNM subsets have been moved to a new stage grouping, according to Dr. Peter Goldstraw of Imperial College, London, and his colleagues on behalf of the IASLC Staging and Prognostic Factors Committee.

Major new proposals

T1 changes: Size cut points have further proliferated in the proposals for the 8th edition, an outgrowth of the emphasis on tumor size in the 7th edition, such that size will now be a descriptor in all T categories, according to the authors. New stage groupings proposed divide stage T1 into T1a, T1b, and T1c, based on the new size cut points of 1 cm and 2 cm. This results in these cases (when associated with the categories N0 and M0) being assigned to stages 1A1, 1A2, and 1A3, respectively, which reflects the statistically different prognosis of these cases.

T3, T4 changes: A new group has been created for the most advanced local disease categories, T3 and T4 associated with N3 disease, but category M0. Such cases will now be classified as stage IIIC, reflecting their worse outcomes than seen in cases involving tumors that remain in stage IIIB. The prognosis for stage IIIC cases is similar to that of stage IVA cases, however the researchers justified the separation, based upon the different treatment approaches used for such cases.

M changes: Although cases with intrathoracic metastatic disease to the contralateral lung or with pleural/pericardial dissemination remain classified as M1a disease, the category M1b will now be assigned to cases with a single metastatic deposit (in one organ) and M1a and M1b cases will be moored to a new stage grouping called IVA. The more common situation of multiple metastatic deposits, usually in more than one organ, will be classified as M1c and staged as IVB. Separation of the M1a and M1b categories was maintained both for further data analysis and because some patients with oligometastatic disease are now receiving more aggressive local therapy in addition to systemic treatment, according to the authors.

Other proposals

A variety of more minor changes to stage groupings has also been proposed, some of which will result in a T descriptor being allocated to a higher stage. In some cases, tumors may be allocated to a different T category entirely, leading to a reclassification of stage. Among the examples given were tumors associated with diaphragmatic invasion to TV, which, when associated with N0 disease, will move from stage IIB to IIA.

Impact on treatment

The relationship of the proposed classification changes to treatment decisions is not direct, the authors stated in their discussion. "Although such changes might raise the issue of whether consequent changes to treatment algorithms are needed, it is important to remind ourselves that stage does not dictate treatment. Stage is one, and perhaps the most important, of several prognostic factors that guide the appropriate treatment option[s] to offer the patient. Any change to established treatment algorithms should be based on clinical judgment informed by prospective trials," they emphasized.

New stage groupings should be used in any trials of novel therapies, they added.

"We hope that the thoracic oncology community finds the proposals of value and that, when accepted, will have a positive impact on the effectiveness of treatment for lung cancer," the researchers concluded.

The research to develop the new proposals was funded by the IASLC, including funds obtained through unrestricted grants obtained from the pharmaceutical industry. The authors reported no other disclosures.

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VIEW ON THE NEWS

Mandatory reading for surgeons

The 8th edition of the TNM staging is upon us. It is the summary of analysis of 90,000 cases and data collected over 11 years. It behooves every thoracic surgeon taking care of patients with lung cancer to familiarize themselves with the new version. The staging proposal is available as an open access article on the Journal of Thoracic Oncology website.

From a statistical viewpoint, this edition fits the data better than previous editions did. However, from a practical application, it is more cumbersome to use routinely in a busy clinic. One hopes that we can soon say, "There's an app for that!" Such interfacing will enhance the application of this edition significantly.

The new edition of the staging system is particularly important for surgeons for two reasons. The first is the formal recognition that patients with oligometastatic disease have a better prognosis than other stage IV disease and may be amenable to multimodality therapies with curative intent, as is currently performed by select clinical teams. The second is the further refinement of stage I disease with respect to tumor size. Combined with the new histologic classification of adenocarcinoma and its proposed integration with the TNM classification, the debate of sublobar vs. lobar resection for stage I NSCLC will become more nuanced. These implications for the practicing thoracic surgeon make the manuscript mandatory reading.

Dr. Sai Yendamuri is chair, department of thoracic surgery, and director, thoracic surgery research laboratory, and a professor of oncology at Roswell Park Cancer Institute, Buffalo, N.Y. He is also the general thoracic editor for Thoracic Surgery News.

Glessen hybrid option for hypoplastic left heart syndrome

BY RICHARD MARK KIRKNER
Frontline Medical News

The classic Norwood palliation for infants with hypoplastic left heart syndrome (HLHS) is well established, but the procedure has drawbacks that include the need for cardiopulmonary bypass with hypothermia and it rules out biventricular correction months later. A hybrid procedure avoids the need for bypass and accommodates short-term biventricular correction, but it has lacked strong evidence.

Researchers from Justus-Liebig University Giessen, Germany, reported on 182 patients with HLHS who had the three-stage Giessen hybrid procedure, noting 10-year survival of almost 80% with almost a third of patients requiring no artery intervention in that time (J Thorac Cardiovasc Surg. 2016 April;151:1112-23).

"In view of the early results and long-term outcome after Giessen hybrid palliation, the hybrid approach has become a reasonable alternative to the conventional strategy to treat neonates with HLHS and variants," wrote Dr. Can Yerebakan and colleagues. "Further refinements are warranted to decrease patient morbidity."

The Giessen hybrid procedure uses a technique to control pulmonary blood flow that is different from the Norwood procedure. The hybrid ap-

Continued on following page

Continued from previous page

proach involves stenting of the arterial duct or prostaglandin therapy to maintain systemic perfusion combined with off-pump bilateral banding of the pulmonary arteries (bPAB) in the neonatal period. The Giessen hybrid operation defers the Norwood-type palliation using cardiopulmonary bypass that involves an aortic arch reconstruction, including a superior cavopulmonary connection or a biventricular correction, if indicated, until the infant is 4-8 months of age.

"In recent years, hybrid treatment has moved from a myth to an alternative modality in a growing number of institutions globally," Dr. Yerebakan and colleagues said.

The hybrid procedure has been used in high-risk patients. One report claimed higher morbidity in the hybrid procedure due to bPAB (Ann Thorac Surg. 2013;96:1382-8). Another study raised concerns about an adequate pulmonary artery rehabilitation at the time of the Fontan operation, the third stage in the hybrid strategy (J Thorac Cardiovasc Surg. 2014;147:706-12).

But with the hybrid approach, patients retain the potential to receive a biventricular correction up to 8 months later without compromising survival, "postponing an immediate definitive decision in the newborn period in comparison with the classic Norwood palliation," Dr. Yerebakan and coauthors noted.

The doctors at the Pediatric Heart Center Giessen treat all types and variants of HLHS with the modified Giessen hybrid strategy. Between 1998 and 2015, 182 patients with HLHS had the Giessen hybrid stage I operation, including 126 patients who received univentricular palliation or a heart transplant.

The median age of stage I recipients was 6 days, and median weight 3.2 kg. The stage II operation was performed at 4.5 months, with a range of 2.9 to 39.5 months, and Fontan completion was established at 33.7 months, with a range of 21 to 108 months.

Median follow-up after the stage I procedure was 4.6 years, and the death rate was 2.5%. After stage II, mortality was 4.9%; no deaths were reported after Fontan completion. Body weight less than 2.5 kg and aortic atresia had no significant effect on survival. Mortality rates were 8.9% between stages I and II and 5.3% between stage II and Fontan completion.

"Cumulative interstage mortality was 14.2%," Dr. Yerebakan and colleagues noted. "At 10 years, the probability of survival is 77.8%."

Also at 10 years, 32.2% of patients were free from further pulmonary artery intervention, and 16.7% needed aortic arch reconstruction.

Two patients required reoperations for aortic arch reconstruction.

With the hybrid approach, patients retain the potential to receive a biventricular correction up to 8 months later without compromising survival, postponing an immediate definitive decision in the newborn period in comparison with the classic Norwood palliation.

Dr. Yerebakan and colleagues suggested several steps to improve outcomes with the hybrid approach: "intense collaboration" with anesthesiology and pediatric cardiology during and after the procedure to risk stratify individual patients; implementation of standards for management of all stages, including out-of-hospital care, in all departments that participate in a case; and liberalized indications for use of MRI before the stage II and Fontan completion.

Among the limitations of the study the authors noted were its retrospective nature and a median follow-up of only 5 years when the center has some cases with up to 15 years of follow-up.

But Dr. Yerebakan and coauthors said they could not determine if the patients benefit from the hybrid treatment in the long-term.

The researchers had no disclosures.

VIEW ON THE NEWS

Dr. Jacques-Pierre Fontaine, FCCP, comments: This research is interesting and impactful. The hybrid operation for HLHS is a new technique not well known by North American cardiothoracic surgeons – especially ones who do not practice pediatric cardiac surgery routinely.

Web app extended survival of lung cancer patients

BY DANIEL M. KELLER
Frontline Medical News

CHICAGO – A simple Web-based mobile application (web-app) improved survival time and quality of life of patients with advanced lung cancer, according to a randomized study presented at the annual meeting of the American Society of Clinical Oncology.

The study was stopped at the planned interim survival analysis that occurred after 121 evaluable patients because of survival benefit favoring the web-app arm. The application, called Moovcare, allowed patients to report symptoms over time and stay in close touch with their care providers after their initial surgery, chemotherapy, or radiation therapy.

The 1-year survival was 75% in the Moovcare arm vs. 49% in the control arm.

DR. DENIS

"The 1-year survival was 75% in the Moovcare vs. 49% in the control arm," said lead author Dr. Fabrice Denis of the Institut Inter-régional de Cancérologie Jean Bernard in LeMans, France, in a press conference.

Dr. Denis identified several reasons why a web-app could be useful in treating patients with lung cancer. Even with more than 1 million lung cancer deaths a year worldwide, there is no standard follow-up, and relapses do not occur on a 3 or 6-month schedule of planned visits. So patients often wait several weeks until their next visit to report symptoms indicative of a relapse. They may also be reluctant to report symptoms because of shame over how they contracted the disease, for example, from smoking. And patients are often hesitant to "bother" the doctor with symptoms between visits. All these reasons can contribute to suboptimal therapy and worse outcomes.

Moovcare was designed to allow patients to report symptoms weekly, facilitating early detection of relapse or dangerous conditions and triggering early supportive care. They compared the web-app to a control of usual, nonpersonalized follow-up in a French multicenter prospective, randomized trial.

Patients (n = 121) with stage II/node-positive to stage IV (90% stage III/IV) nonprogressive small cell or non–small cell lung cancer were randomly assigned 1:1 to the two arms of the trial. They had to have Internet access, prior experience with email, performance status of 0-2, and an initial symptom score less than 7.

Patients could be taking tyrosine kinase inhibitors or on maintenance therapy.

Monitoring visits were the same for both groups every 3 months or more frequently. Patients in the control arm received more frequent computed tomographic (CT) imaging than did ones in the web-app arm, and CT scans could be performed at any time in either group based on the investigator's clinical judgment, or in the case of the web-app, as suggested by patient report in the algorithm.

The median follow up was 9 months. Relapse rates were close to 50% for both groups. The 1-year survival of 75% in the Moovcare to 49% in the control arm gave a 1-year absolute survival increase of 26%. Median survival was 19 months vs. 12 months, a 7-month improvement in median survival for the Moovcare arm. The hazard ratio for death in the web-app arm, compared with the control arm was 0.325 (95% confidence interval, 0.157-0.672; $P = .0025$).

When they relapsed, 77% of patients in the web-app arm had a good performance status, compared with 33% in the control arm. "This led to 74% of patients receiving optimal therapy in the Moovcare arm vs. 33% in the control arm," Dr. Denis said. "And the number of imaging [procedures] was reduced by 50% per patient per year."

Overall quality of life was better in the web-app arm, as assessed using standard quality of life questionnaires.

Moovcare works by having patients or their relatives report 12 symptoms weekly (for example, asthenia, cough, dyspnea, anorexia, etc.) using a smartphone, tablet, or computer. An algorithm analyzes an association of symptoms and triggers email alerts to health care providers if relapse or dangerous medical conditions may be occurring. Providers follow up alerts by phone and schedule visits and imaging. "The sensitivity of the algorithm was high and was validated in two prospective studies," Dr. Denis said. Sensitivity was 86%-100%.

Moovcare allowed earlier detection of relapse and improved overall survival for three reasons. "It allowed higher performance status at relapse, leading to more optimal therapy for relapsing patients. Dangerous medical conditions were detected earlier and treated earlier. It favored earlier supportive care, which improved quality of life. Less imaging was needed and performed at the right time," Dr. Denis said.

Patients were monitored on a weekly basis, allowing more personalized care. The Moovcare web-app has been evaluated prospectively in about 300 patients, providing a high level of evidence of its utility in improving outcomes for patients with advanced lung cancer.

Press conference moderator Dr. Patricia Ganz commented that Moovcare is an example of a new way to improve the delivery of high-quality care to patients. "If we had a drug or some new intervention that caused this level of survival benefit, wouldn't we want to go out and use it?" she asked. "This is a tremendous advance. This is personalized medicine. This is really tailoring it to the patient, and you can see how simple it is to collect this kind of data from the patient and then bring them in in between what would have been a scheduled visit."

Dr, Ganz said the app overcomes putting off reporting symptoms until the next visit and reluctance to "bother the doctor."

Another advantage of the app is that it alerts the health care team to potential problems and prompts them to "use tests when appropriate, not on a schedule, [which] leads to avoidance of waste in the follow-up of care of our patients," she said.

Wedge resection beats SBRT for stage I lung cancer treatment

BY RICHARD PIZZI
Frontline Medical News

BALTIMORE – Surgical resection of early-stage non–small cell lung cancer afforded a superior survival advantage for patients than did stereotactic body radiation therapy (SBRT), based on study results presented at the 2016 annual meeting of the American Association for Thoracic Surgery.

While an increasing number of non–small cell lung cancer patients have been treated with SBRT, it appears that surgery may still be the better option.

"Frankly, I was surprised to see such a big difference between SBRT and wedge resection," said Dr. Walter Weder, professor of surgery at University Hospital Zürich, in an interview at AATS 2016.

Dr Weder served as a discussant on the paper, and said the results confirm that surgeons should be involved in discussions with patients when they are considering treatment options. "Surgery can be done safely... and patients should know this information," he said.

Dr. Weder reported no relevant financial disclosures.

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FRONTLINE MEDICAL NEWS

To watch the interview, search "Weder" at www.chestphysician.org.

Palliation benefits extend to patients' caregivers

BY JESSICA CRAIG
Frontline Medical News

Introducing palliative care in combination with standard oncology care immediately following a cancer diagnosis results in improved quality of life and lower incidence of depression for caregivers of cancer patients.

"The integration of palliative care can improve patient care but the evidence is lacking about whether or not there are benefits [for] caregivers," Dr. Areej El-Jawahri of Massachusetts General Hospital, Boston, said in a presscast leading up to the annual meeting of the American Society of Clinical Oncology.

"While patients receive a direct benefit from early palliative care, their caregivers experience a positive downstream effect, which may make it easier for them to care for their loved ones."

"This study suggests that early palliative care creates a powerful positive feedback loop in families facing cancer. While patients receive a direct benefit from early palliative care, their caregivers experience a positive downstream effect, which may make it easier for them to care for their loved ones," she said.

Investigators enrolled 275 family caregivers of patients newly diagnosed with incurable lung or gastrointestinal cancers. Patients were randomly assigned to receive early palliative care in addition to standard oncology care or to receive standard oncology care alone.

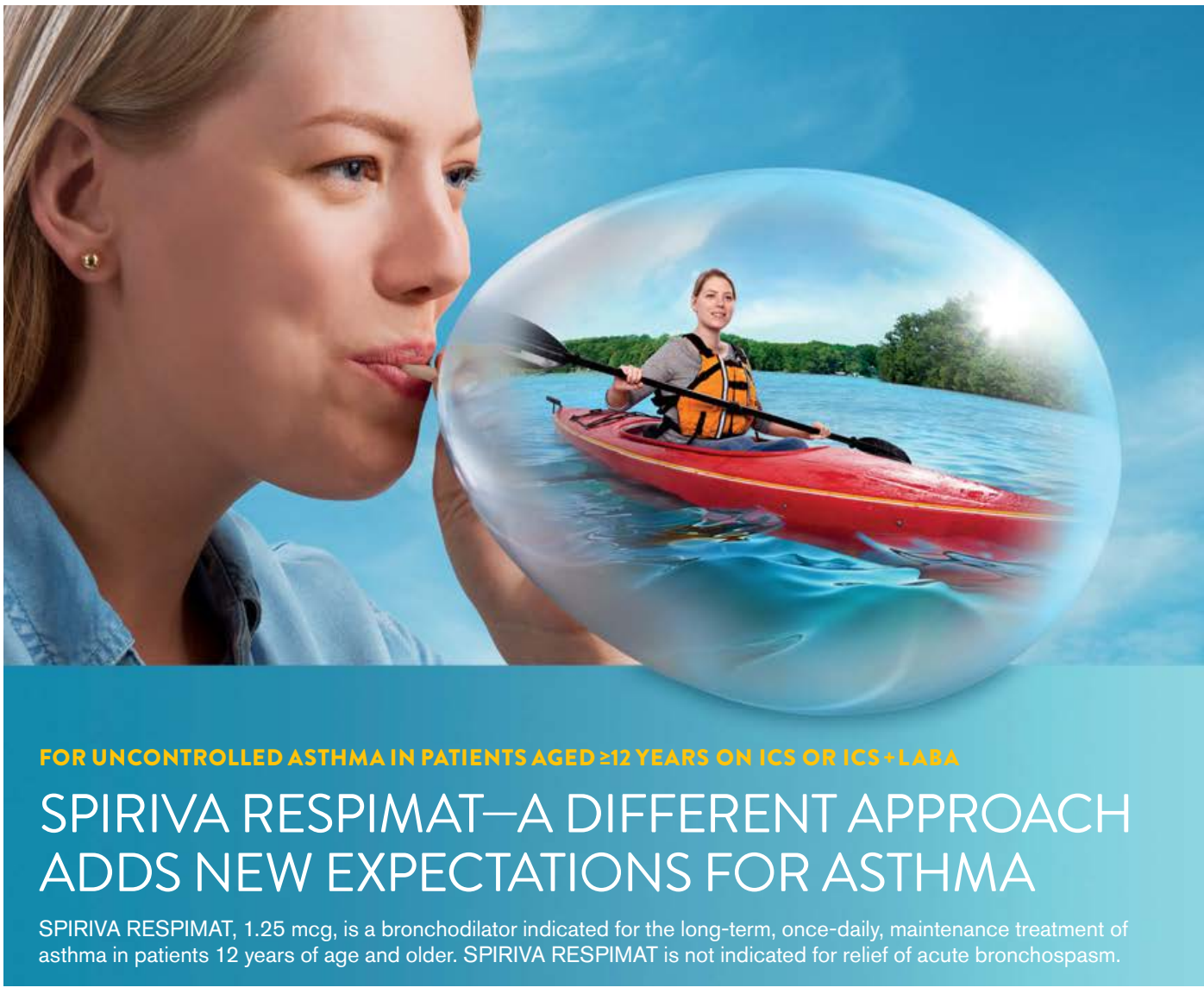
Palliative care involved a multifaceted team including nurses, social workers, and psychologists.

The palliative care intervention was patient focused.

Caregivers, who were defined as a relative or friend identified by the patient as the primary caregiver, were not required to attend palliative care

VIEW ON THE NEWS

Dr. W. Michael Alberts, Master FCCP, comments: 'Early' palliative care (I prefer the term supportive care) has been shown to be of benefit to patients diagnosed with lung cancer. Proven benefit was welcome news to clinicians in the field who have now begun to incorporate this treatment in many, if not most, patients. In addition to the patient, the caregivers may be adversely affected by the diagnosis of lung cancer and its treatment. It is great to see that the benefits of 'early' supportive care accrue to caregivers, as well as to the patient. This is one more reason to get supportive care involved early.



appointments. However, about 50% of caregivers did attend, according to Dr. El-Jawahri.

At the time of enrollment and then at the time points of 12 and 14 weeks post enrollment, caregivers completed standard questionnaires. These included the 36-Item Short Form Health Survey and the Hospital Anxiety and Depression Scale. Both of these questionnaires assessed quality of life and mood.

Twelve weeks after the cancer diagnosis, those caregivers who received early palliative care reported experiencing significantly lower depression symptoms.

At the same time, their vitality and social functioning had improved.

For patients who did not receive early palliative care, their caregivers' vitality and social functioning decreased.

"This is the first study showing a positive impact of a patient-focused palliative care intervention on family caregivers," said Dr. El-Jawahri.

The results of this study "really point out that we have so many ways to help our patients and their families," Dr. Julie Vose, president of ASCO, commented during the presscast.

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2015-2016 flu season milder than past 3 years

BY MICHELE G. SULLIVAN
Frontline Medical News

The 2015-2016 flu season was less severe than the last three seasons, with a lower hospitalization rate and fewer pediatric deaths.

Cases of influenza appeared later in the season than typically seen, and activity didn't peak until March, Stacy L. Davlin, Ph.D., wrote in Morbidity and Mortality report (MMWR 2016; 22:567-75)

"During the most recent 18 influenza seasons, only two other seasons have peaked in March (2011-2012 and 2005-2006)," wrote Dr. Davlin, an epidemiologist at the Centers for Disease Control and Prevention, Atlanta.

"Although summer influenza activity in the United States typically is low, influenza cases and outbreaks have occurred during summer

months, and clinicians should remain vigilant in considering influenza in the differential diagnosis of summer respiratory illnesses," Dr. Davlin said.

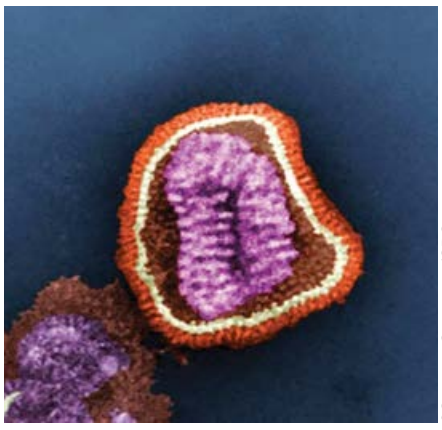
The most common influenza virus of the last season was A(H1N1), which accounted for about half of cases in those aged 5-24 years, and about 70% of cases in those younger than 5 years and those 65 years and older.

Three novel viruses were seen as well: variants of A(H1N1), A(H1N2), and A(H3N2). The A(H1N1) variant occurred in a Minnesota resident who lived and worked in an area of swine farming, but who denied direct contact with pigs. The A(H3N2) variant occurred in a New Jersey resident who reported visiting a farm shortly before symptom onset. There was no evidence of human-to-human transmission. Both recovered fully without hospitalization. The A(H1N2) variant occurred in a Minnesota resident who was hospitalized but who recovered.

The CDC tested 2,408 viral specimens for susceptibility to antiviral medications. Among the 2,193 A(H1N1) specimens, less than 1% were resistant to oseltamivir and peramivir. All were susceptible to zanamivir. However, the testing found persistent high levels of A viruses resistant to amantadine and rimantadine.

Amantadine is not effective against B virus strains. Therefore, CDC does not recommend the use of amantadine as an anti-influenza medication.

Reports of influenza first exceeded the 2.1% baseline level in the week ending Dec. 26, 2015, and remained elevated for the next 17 weeks, with a peak of 3.6% of all outpatient visits in the week ending March 12, according to the U.S. Outpatient Influenza-Like Illness Surveillance Network (ILINet).



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Reports of influenza first exceeded 2.1% in the week ending Dec. 26, 2015, and peaked at 3.6% in the week ending March 12.

Hospitalization rate for influenza-like illness was highest in those aged 65 years and older (85/100,000), and lowest in those aged 5-17 years (10/100,000). About 92% of adults hospitalized for flu-like illness had at least one underlying medical comorbidity, including obesity (42%), cardiovascular disease (40%), and metabolic disorders (38%). Almost half of children (48%) also had medical comorbidities, including asthma or other reactive airway disease (22%) and neurologic disorders (18%).

The percentage of deaths attributed to pneumonia and influenza peaked at 8% during the week ending March 19. The death rate in the last 5 years ranged from 9% in 2011-2012 to 11% in 2012-2013. Of this season's deaths, 74 occurred in children. There were 171 pediatric deaths in 2012-2013, 111 in 2013-2014, and 148 in 2014-2015.

As a CDC employee, Dr. Davlin had no financial disclosures.

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If you'd like to attend CHEST Annual Meeting 2016 but have trouble scheduling time away from your practice, consider the 1-day registration. Register for any given day, Sunday through Wednesday. Or, attend for the weekend by registering for a postgraduate course on Saturday and 1 day on Sunday.

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- Pulmonary Medicine 2016: Year in Review and Clinical Update
- Sleep Medicine 2016: Year in Review and Clinical Update
- 24th Annual Assembly of the American Association for Bronchology and Interventional Pulmonology

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Learn more about Los Angeles at discoverlosangeles.com, and find information about CHEST 2016 at chestmeeting.chestnet.org.

PRESIDENT'S REPORT: Location, location, location!

BY HEATHER M. NASH, CMP, AND DR. BARBARA A. PHILLIPS, MSPH, FCCP

Do you ever wonder how CHEST decides where to have its annual meeting? It's a science! We know that venue is an important consideration for busy clinicians who are trying to decide whether to invest time and money in attending a national meeting. Evaluation of criteria that determine the attractiveness of a given location for a national meeting is a job for professionals!

At CHEST, we are very fortunate to work with Heather Nash, CMP, who is the Senior Director, Meetings and Training Center Operations. She and her talented meetings team work together to choose a top-notch destination for the CHEST Annual Meeting.

The site selection for an annual meeting is a very important decision an association makes for its members. There is a variety of factors considered in making this decision, and the site selection process begins approximately 5-7 years in advance. Why so early, you might ask. The size of the CHEST Annual Meeting is the answer!

Our annual meeting requires a significant amount of meeting, exhibits, ballroom, and public foyer space. Additionally, the host city needs a minimum of 3,000 hotel rooms in the vicinity of the Convention Center. What this means is that the CHEST Annual Meeting does not fit into all convention centers and cities within the United States and Canada. Plus, other important criteria that are also considered are cost, travel, weather, and the amenities that a destination offers.

The site selection process starts with each destination's Convention and Visitors Bureau that is presented with a Request for Proposal, which includes a list of all the CHEST Annual Meeting specifications, requirements, and preferred dates. Based on those specifications, each city will compile a proposal of its full offerings, including meeting space, hotels, air and ground transportation, weather, cost, and key amenities of the destination. The puzzle that each city goes through is to determine whether the destination has all of the requirements needed by CHEST and to submit a complete proposal. It's fierce competition out there, which is why the process must start 5-7 years prior. The last step is to compile a site selection report that outlines, in order of priority, all components that CHEST needs to create a short list of locations and propose a final decision.

Why is the convention center size so important? The CHEST Meeting Director must determine whether a certain venue and city can accommodate the CHEST Annual Meeting. A few key factors that are reviewed include exhibit space; a minimum of 300,000+ gross square feet, 30+ flexible size meeting rooms that can accommodate 75-400 people each for educational sessions, opening keynote session space for

Continued on following page

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2,500 people, a Simulation Center space, not to mention the additional needs for registration, self-study stations, games, and other e-learning opportunities.

Many times, the cities with the larger convention centers attract CHEST (Chicago, New Orleans, Toronto, San Francisco, and Los Angeles). However, CHEST has had some of its strongest attendance in cities with somewhat smaller convention centers (Montreal, Austin, Honolulu, and Vancouver).

Of course, there are the other aspects of an annual meeting that are very important to clinicians, guests, and attendees. How easy is it to get a flight at a reasonable cost? How close are the hotels and what are the room rates of the official meeting hotels? Can I walk to the convention center or do we need to get on a bus? Can I walk to a restaurant after a full day of sessions? These are just a few questions we receive often by our CHEST Help Team representatives. We track these types of questions so that when we engage a prospective destination, these questions are answered in the final proposal and site selection report.

The **CHEST Annual Meeting 2016** will be held in Los Angeles, California. Los Angeles was confirmed as the location in 2011, based upon the improved infrastructure in the downtown Los Angeles area and the renovations made within the Los Angeles Convention Center.

The infrastructure mentioned is an area called L.A. LIVE, which is the sports and entertainment district that surrounds the STAPLES Center and Microsoft Theater, JW Marriott, and the Los Angeles Convention Center. The campus features sports and music venues, nightclubs, restaurants, a bowling alley, the GRAMMY museum, and movie theaters. L.A. LIVE is the premier destination for live entertainment in downtown Los Angeles and very walkable!

We hope you have learned a bit about the process we adhere to in the site selection process for the CHEST Annual Meeting, and we look forward to welcoming you in October.

See you in Los Angeles!

CHEST Leadership Attends Conference in Rome

Dr. Francesco de Blasio, FCCP, Chair of the CHEST Council of Global Governors; is shown here with Dr. Barbara Phillips, FCCP, CHEST President. They attended the International Conference on Respiratory Pathophysiology, Sleep, and Breathing in Rome, Italy, as members of the Scientific Committee.

CHEST Foundation: Training village doctors in China

In 2012, Dr. Renli Qiao, FCCP, won the D. Robert McCaffree, MD, Master FCCP Humanitarian Award for his critical work with village doctors in rural China. Because medical schools in China are located in larger metropolitan areas where graduates are likely to stay, medical resources are unevenly distributed across the country. Physicians with shortened medical education often staff rural hospitals, and smaller villages usually house a single village doctor with a high-school diploma and 3-6 months of medical training.

Inspired by his work with the China California Heart Watch (CCHW), Dr. Qiao created a program to train rural medical professionals so that their efforts would have a sustaining impact on the care that residents of these villages receive. Volunteer physicians traveled through as many villages on foot to spend several days in each village where they would see about 250 villagers a day. In these villages, the doctors were also able to perform heart examinations for hundreds of children in the village schools. The team observed that although hypertension is the leading cause of death in China and the antihypertensive drugs are relatively affordable, there is a high incidence of hypertension, and up to 95% of patients with hypertension were never diagnosed or treated.

Realizing the need to train doctors on the importance of preventive care, early diagnoses, and treatment of hypertension, Dr. Qiao led the initiative to educate thousands of doctors in the Yunnan province. His model involved 2-day seminars and included participatory workshops, lectures, group collaboration, and the dissection of clinical cases. Dr. Qiao's effort not only improved the lives of thousands of patients but also achieved a lasting model to educate rural doctors. He is now aiding in the China-CHEST PCCM program efforts to establish PCCM as a subspecialty in China.

Dr. Qiao helping a patient in rural China.

CHEST Past President honored

The Lung Association of Saskatchewan has conferred its highest award on Dr. Darcy Marciniuk, FCCP. The Lifetime Achievement Award recognizes 25 years of outstanding service by Dr. Marciniuk to improving respiratory health in Saskatchewan. Dr. Marciniuk is currently associate vice president of research (Acting) at the University of Saskatchewan, Canada, in addition to continuing to serve as professor of medicine in the division of respirology, critical care, and sleep medicine.

Dr. Marciniuk led the development of both respiratory services and chronic disease management in general in the Saskatoon Health Region, which is now spreading to the province as a whole. He began the LiveWell program that started with respiratory health and was used as a model to expand the chronic disease management program to other health areas. He was a leader in the development of the Lung Health Institute and is currently spearheading the establishment of a respiratory research center at the University of Saskatchewan. He has done extensive research in the area of chronic obstructive pulmonary disease, for which he is nationally and internationally recognized with more than 100 peer-reviewed publications. Dr. Marciniuk is currently a leader in the CHEST initiative to develop a national respirology training program in China, which is being implemented in collaboration with the Chinese government.

CHEST congratulates Dr. Marciniuk on this prestigious honor.

Ms. Pat Smith, Chair of the Lung Association of Saskatchewan volunteer board, presents the 2016 Lifetime Achievement Award to Dr. Darcy Marciniuk at the Respirology State of the Art Conference, Saskatoon, May 28, 2016.

This month in *CHEST*: Editor's picks

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

EDITORIAL

Burnout syndrome in ICU caregivers: Time to extinguish! *By Dr. S. Pastores, FCCP*

COMMENTARY

An Official Critical Care Societies Collaborative Statement – Burnout syndrome in critical care health-care professionals: A call for action. *By Dr. M. Moss et al.*

GIANTS IN CHEST MEDICINE

Neil R. MacIntyre, MD, FCCP. *By Dr. Lisa K. Moores, FCCP*

ORIGINAL RESEARCH

Protective cardiovascular effect of sleep apnea severity in obesity hypoventilation syndrome. *By Dr. J. R. Masa et al.*

Treprostinil administered to treat pulmonary arterial hypertension using a fully implantable programmable intravascular delivery system: Results of the DeliVery for PAH Trial. *By Dr. R. C. Bourge et al.*

Improving quality of acute asthma care in US hospitals: Changes between 1999-2000 and 2012-2013. *By Dr. K. Hasegawa et al.*

NUCALA
THE FIRST TARGETED ANTI-INTERLEUKIN 5 THERAPY FOR SEVERE ASTHMA WITH AN EOSINOPHILIC PHENOTYPE

NUCALA is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older with an eosinophilic phenotype.

- NUCALA is not indicated for treatment of other eosinophilic conditions.
- NUCALA is not indicated for the relief of acute bronchospasm or status asthmaticus.

Important Safety Information

CONTRAINDICATIONS

NUCALA should not be administered to patients with a history of hypersensitivity to mepolizumab or excipients in the formulation.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions
Hypersensitivity reactions (eg, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred following administration of NUCALA. These reactions generally occur within hours of administration but in some instances can have a delayed onset (ie, days). In the event of a hypersensitivity reaction, NUCALA should be discontinued.

Acute Asthma Symptoms or Deteriorating Disease
NUCALA should not be used to treat acute asthma symptoms, acute exacerbations, or acute bronchospasm.

Opportunistic Infections: Herpes Zoster
In controlled clinical trials, 2 serious adverse reactions of herpes zoster occurred in subjects treated with NUCALA compared to none in placebo. Consider varicella vaccination if medically appropriate prior to starting therapy with NUCALA.

Reduction of Corticosteroid Dosage
Do not discontinue systemic or inhaled corticosteroids (ICS) abruptly upon initiation of therapy with NUCALA. Decreases in corticosteroid doses, if appropriate, should be gradual and under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Parasitic (Helminth) Infection
It is unknown if NUCALA will influence a patient's response against parasites. Treat patients with pre-existing helminth infections before initiating therapy with NUCALA. If patients become infected while receiving treatment with NUCALA and do not respond to anti-helminth treatment, discontinue treatment with NUCALA until infection resolves.

ADVERSE REACTIONS

The most common adverse reactions (≥3% and more common than placebo) reported in the first 24 weeks of 2 clinical trials with NUCALA (and placebo) were: headache, 19% (18%); injection site reaction, 8% (3%); back pain, 5% (4%); fatigue, 5% (4%); influenza, 3% (2%); urinary tract infection, 3% (2%); abdominal pain upper, 3% (2%); pruritus, 3% (2%); eczema, 3% (<1%); and muscle spasm, 3% (<1%).

NUCALA IS PROVEN TO:

- **Reduce exacerbations* by 53%** (NUCALA: 0.83/year; placebo: 1.74/year, *P*<0.001)[1]
- **Reduce daily OCS dose while maintaining asthma control** (*P*=0.008)[1]
- **Improve quality of life (SGRQ) with a responder rate of 71% for NUCALA compared with 55% for placebo** (odds ratio of 2.1; 95% CI: 1.3, 3.2)†
  - Statistical hierarchy was not met, endpoint is exploratory, and results are descriptive only[1]

In a 32-week study of patients with severe asthma with an eosinophilic phenotype, NUCALA (n=194) and placebo (n=191), each added to high-dose ICS and at least 1 other controller with or without OCS and dosed once every 4 weeks, were compared to evaluate the frequency of exacerbations. In a 24-week study of 135 patients with severe asthma with an eosinophilic phenotype, NUCALA and placebo were each added to high-dose ICS and at least 1 other controller and dosed once every 4 weeks to compare the percent reduction in daily OCS dose (weeks 20 to 24) while maintaining asthma control.[1]

ICS=inhaled corticosteroids; OCS=oral corticosteroids; SGRQ=St. George's Respiratory Questionnaire.

*Defined as the worsening of asthma that required use of oral/systemic corticosteroids and/or hospitalization and/or emergency department visits; for patients requiring maintenance oral/systemic corticosteroids, exacerbations were defined as at least double the existing maintenance dose for at least 3 days.[1]

†The SGRQ is a validated measure of health impairment for chronic respiratory diseases and is able to address the impact asthma has on a patient's quality of life. Response is defined as a change in score of 4 or more as threshold.[1]

Visit **NUCALAhcp.com** for more information, including patient access programs.

Important Safety Information (cont'd)

ADVERSE REACTIONS (cont'd)

Systemic Reactions, including Hypersensitivity Reactions: In 3 clinical trials, 10% of subjects who received NUCALA experienced systemic (allergic and nonallergic) and local site reactions compared to 7% in the placebo group. Systemic allergic/hypersensitivity reactions were reported by 1% of subjects who received NUCALA compared to 2% of subjects in the placebo group. Manifestations included rash, pruritus, headache, and myalgia. Systemic nonallergic reactions were reported by 2% of subjects who received NUCALA and 3% of subjects in the placebo group. Manifestations included rash, flushing, and myalgia. A majority of the systemic reactions were experienced on the day of dosing.

Injection Site Reactions: Injection site reactions (eg, pain, erythema, swelling, itching, and burning sensation) occurred at a rate of 8% in subjects treated with NUCALA compared with 3% in subjects treated with placebo.

USE IN SPECIFIC POPULATIONS

A pregnancy exposure registry monitors pregnancy outcomes in women exposed to NUCALA during pregnancy. Healthcare providers can enroll patients or encourage patients to enroll themselves by calling 1-877-311-8972 or visiting www.mothertobaby.org/asthma.

The data on pregnancy exposures from the clinical trials are insufficient to inform on drug-associated risk. Monoclonal antibodies, such as mepolizumab, are progressively transported across the placenta in a linear fashion as pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and third trimesters of pregnancy.

Reference: 1. Data on file, GSK.

Please see Brief Summary of Prescribing Information for NUCALA on the following pages.

Nucala® (mepolizumab) for Subcutaneous Injection 100 mg/vial

BRIEF SUMMARY

NUCALA®
(mepolizumab) for injection, for subcutaneous use
The following is a brief summary only; see full Prescribing Information for complete product information.

INDICATIONS AND USAGE
NUCALA is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. *[See Clinical Studies of full Prescribing Information.]*

Limitations of Use
- NUCALA is not indicated for treatment of other eosinophilic conditions.
- NUCALA is not indicated for the relief of acute bronchospasm or status asthmaticus.

CONTRAINDICATIONS
NUCALA should not be administered to patients with a history of hypersensitivity to mepolizumab or excipients in the formulation.

WARNINGS AND PRECAUTIONS
Hypersensitivity Reactions
Hypersensitivity reactions (e.g., angioedema, bronchospasm, hypotension, urticaria, rash) have occurred following administration of NUCALA. These reactions generally occur within hours of administration, but in some instances can have a delayed onset (i.e., days). In the event of a hypersensitivity reaction, NUCALA should be discontinued *[see Contraindications]*.

Acute Asthma Symptoms or Deteriorating Disease
NUCALA should not be used to treat acute asthma symptoms or acute exacerbations. Do not use NUCALA to treat acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with NUCALA.

Opportunistic Infections: Herpes Zoster
In controlled clinical trials, 2 serious adverse reactions of herpes zoster occurred in subjects treated with NUCALA compared with none in placebo [*see Adverse Reactions]*. Consider varicella vaccination if medically appropriate prior to starting therapy with NUCALA.

Reduction of Corticosteroid Dosage
Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with NUCALA. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Parasitic (Helminth) Infection
Eosinophils may be involved in the immunological response to some helminth infections. Patients with known parasitic infections were excluded from participation in clinical trials. It is unknown if NUCALA will influence a patient's response against parasitic infections. Treat patients with pre-existing helminth infections before initiating therapy with NUCALA. If patients become infected while receiving treatment with NUCALA and do not respond to anti-helminth treatment, discontinue treatment with NUCALA until infection resolves.

ADVERSE REACTIONS
The following adverse reactions are described in greater detail in other sections:
- Hypersensitivity reactions *[see Warnings and Precautions]*
- Opportunistic infections: herpes zoster *[see Warnings and Precautions]*

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.

A total of 1,327 subjects with asthma were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks' duration (Trials 1, 2, and 3). Of these, 1,192 had a history of 2 or more exacerbations in the year prior to enrollment despite regular use of high-dose inhaled corticosteroids plus an additional controller(s) (Trials 1 and 2), and 135 subjects required daily oral corticosteroids in addition to regular use of high-dose inhaled corticosteroids plus an additional controller(s) to maintain asthma control (Trial 3). All subjects had markers of eosinophilic airway inflammation *[see Clinical Studies of full Prescribing Information]*. Of the subjects enrolled, 59% were female, 85% were white, and subjects ranged in age from 12 to 82 years. Mepolizumab was administered subcutaneously or intravenously once every 4 weeks; 263 subjects received NUCALA (mepolizumab 100 mg subcutaneous [SC]) for at least 24 weeks. Serious adverse events that occurred in more than 1 subject and in a greater percentage of subjects treated with NUCALA (n = 263) than placebo (n = 257) included 1 event, herpes zoster (2 subjects vs. 0 subjects, respectively). Approximately 2% of subjects receiving NUCALA withdrew from clinical trials due to adverse events compared with 3% of subjects receiving placebo.

The incidence of adverse reactions in the first 24 weeks of treatment in the 2 confirmatory efficacy and safety trials (Trials 2 and 3) with NUCALA is shown in Table 1.

Table 1. Adverse Reactions with NUCALA with Greater than or Equal to 3% Incidence and More Common than Placebo in Subjects with Asthma (Trials 2 and 3)

Adverse Reaction	NUCALA (Mepolizumab 100 mg Subcutaneous) (n = 263) %	Placebo (n = 257) %
Headache	19	18
Injection site reaction	8	3
Back pain	5	4
Fatigue	5	4
Influenza	3	2
Urinary tract infection	3	2
Abdominal pain upper	3	2
Pruritus	3	2
Eczema	3	<1
Muscle spasms	3	<1

52-Week Trial
Adverse reactions from Trial 1 with 52 weeks of treatment with mepolizumab 75 mg intravenous (IV) (n = 153) or placebo (n = 155) and with greater than or equal to 3% incidence and more common than placebo and not shown in Table 1 were: abdominal pain, allergic rhinitis, asthenia, bronchitis, cystitis, dizziness, dyspnea, ear infection, gastroenteritis, lower respiratory tract infection, musculoskeletal pain, nasal congestion, nasopharyngitis, nausea, pharyngitis, pyrexia, rash, toothache, viral infection, viral respiratory tract infection, and vomiting. In addition, 3 cases of herpes zoster occurred in subjects treated with mepolizumab 75 mg IV, compared with 2 subjects in the placebo group.

Systemic Reactions, including Hypersensitivity Reactions
In Trials 1, 2, and 3 described above, the percentage of subjects who experienced systemic (allergic and non-allergic) and local site reactions was 7% in the placebo group and 10% in the group receiving NUCALA. Systemic allergic/hypersensitivity reactions were reported by 2% of subjects in the placebo group and 1% of subjects in the group receiving NUCALA. The most commonly reported manifestations of systemic allergic/hypersensitivity reactions reported in the group receiving NUCALA included rash, pruritus, headache, and myalgia. Systemic non-allergic reactions were reported by 2% of subjects in the group receiving NUCALA and 3% of subjects in the placebo group. The most commonly reported manifestations of systemic non-allergic reactions reported in the group receiving NUCALA included rash, flushing, and myalgia. A majority of the systemic reactions in subjects receiving NUCALA (5/7) were experienced on the day of dosing.

Injection Site Reactions
Injection site reactions (e.g., pain, erythema, swelling, itching, burning sensation) occurred at a rate of 8% in subjects treated with NUCALA compared with 3% in subjects treated with placebo.

Long-Term Safety
Nine hundred ninety-eight (998) subjects have received NUCALA in ongoing open-label extension studies, during which additional cases of herpes zoster have been reported. The overall adverse event profile was similar to the asthma trials described above.

Immunogenicity
Overall, 15/260 (6%) subjects treated with NUCALA developed anti-mepolizumab antibodies. The reported frequency may underestimate the actual frequency due to lower assay sensitivity in the presence of high drug concentration. Neutralizing antibodies were detected in 1 subject receiving mepolizumab. Anti-mepolizumab antibodies slightly increased (approximately 20%) the clearance of mepolizumab. There was no evidence of a correlation between anti-mepolizumab antibody titers and change in eosinophil level. The clinical relevance of the presence of anti-mepolizumab antibodies is not known.

The data reflect the percentage of patients whose test results were positive for antibodies to mepolizumab in specific assays. The observed incidence of antibody positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease.

DRUG INTERACTIONS
Formal drug interaction trials have not been performed with NUCALA.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to NUCALA during pregnancy. Healthcare providers can enroll patients or encourage patients to enroll themselves by calling 1-877-311-8972 or visiting www.mothertobaby.org/asthma.

Risk Summary
The data on pregnancy exposure from the clinical trials are insufficient to inform on drug-associated risk. Monoclonal antibodies, such as mepolizumab, are transported across the placenta in a linear fashion as pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and third trimester of pregnancy. In a prenatal and postnatal development study conducted in cynomolgus monkeys, there was

no evidence of fetal harm with IV administration of mepolizumab throughout pregnancy at doses that produced exposures up to approximately 30 times the exposure at the maximum recommended human dose (MRHD) of 100 mg SC *[see Data]*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-Fetal Risk: In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

Data

Animal Data: In a prenatal and postnatal development study, pregnant cynomolgus monkeys received mepolizumab from gestation days 20 to 140 at doses that produced exposures up to approximately 30 times that achieved with the MRHD (on an AUC basis with maternal IV doses up to 100 mg/kg once every 4 weeks). Mepolizumab did not elicit adverse effects on fetal or neonatal growth (including immune function) up to 9 months after birth. Examinations for internal or skeletal malformations were not performed. Mepolizumab crossed the placenta in cynomolgus monkeys. Concentrations of mepolizumab were approximately 2.4 times higher in infants than in mothers up to day 178 postpartum. Levels of mepolizumab in milk were less than or equal to 0.5% of maternal serum concentration.

In a fertility, early embryonic, and embryo-fetal development study, pregnant CD-1 mice received an analogous antibody, which inhibits the activity of murine interleukin-5 (IL-5), at an IV dose of 50 mg/kg once per week throughout gestation. The analogous antibody was not teratogenic in mice. Embryo-fetal development of IL-5–deficient mice has been reported to be generally unaffected relative to wild-type mice.

Lactation

Risk Summary

There is no information regarding the presence of mepolizumab in human milk, the effects on the breastfed infant, or the effects on milk production. However, mepolizumab is a humanized monoclonal antibody (IgG1 kappa), and immunoglobulin G (IgG) is present in human milk in small amounts. Mepolizumab was present in the milk of cynomolgus monkeys postpartum following dosing during pregnancy *[see Use in Specific Populations]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NUCALA and any potential adverse effects on the breastfed infant from mepolizumab or from the underlying maternal condition.

Pediatric Use

The safety and efficacy in pediatric patients younger than 12 years have not been established. A total of 28 adolescents aged 12 to 17 years with asthma were enrolled in the phase 3 studies. Of these, 25 were enrolled in the 32-week exacerbation trial (Trial 2) and had a mean age of 14.8 years. Subjects had a history of 2 or more exacerbations in the previous year despite regular use of high-dose inhaled corticosteroids plus an additional controller(s) with or without oral corticosteroids and had blood eosinophils of greater than or equal to 150 cells/mcL at screening or greater than or equal to 300 cells/mcL within 12 months prior to enrollment. *[See Clinical Studies of full Prescribing Information.]* Subjects had a reduction in the rate of exacerbations that trended in favor of mepolizumab. Of the 19 adolescents who received mepolizumab, 9 received NUCALA and the mean apparent clearance in these subjects was 35% less than that of adults. The adverse event profile in adolescents was generally similar to the overall population in the phase 3 studies *[see Adverse Reactions]*.

Geriatric Use

Clinical trials of NUCALA did not include sufficient numbers of subjects aged 65 years and older that received NUCALA (n = 38) to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy. Based on available data, no adjustment of the dosage of NUCALA in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

OVERDOSAGE

Single doses of up to 1,500 mg have been administered intravenously to subjects in a clinical trial with eosinophilic disease without evidence of dose-related toxicities.

There is no specific treatment for an overdose with mepolizumab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of mepolizumab. Published literature using animal models suggests that IL-5 and eosinophils are part of an early inflammatory reaction at the site of tumorigenesis and can promote tumor rejection. However, other reports indicate that eosinophil infiltration into tumors can promote tumor growth. Therefore, the malignancy risk in humans from an antibody to IL-5 such as mepolizumab is unknown.

Male and female fertility were unaffected based upon no adverse histopathological findings in the reproductive organs from cynomolgus monkeys treated with mepolizumab for 6 months at IV doses up to 100 mg/kg once every 4 weeks (approximately 70 times the MRHD on an AUC basis). Mating and reproductive performance were unaffected in male and female CD-1 mice treated with an analogous antibody, which inhibits the activity of murine IL-5, at an IV dose of 50 mg/kg once per week.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions (e.g., angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of NUCALA. Instruct patients to contact their physicians if such reactions occur.

Not for Acute Symptoms or Deteriorating Disease

Inform patients that NUCALA does not treat acute asthma symptoms or acute exacerbations. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with NUCALA.

Opportunistic Infections: Herpes Zoster

Inform patients that herpes zoster infections have occurred in patients receiving NUCALA and where medically appropriate, inform patients varicella vaccination should be considered before starting treatment with NUCALA.

Reduction of Corticosteroid Dosage

Inform patients to not discontinue systemic or inhaled corticosteroids except under the direct supervision of a physician. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Pregnancy Exposure Registry

Inform women there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to NUCALA during pregnancy and that they can enroll in the Pregnancy Exposure Registry by calling 1-877-311-8972 or by visiting www.mothertobaby.org/asthma *[see Use in Specific Populations]*.

NUCALA is a registered trademark of the GSK group of companies.

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Philadelphia, PA 19112
U.S. License Number 1727

Distributed by

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Research Triangle Park, NC 27709

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NetWorks: ACOS, airway clearance therapies, early mobilization

Airways Disorders

The asthma COPD overlap syndrome: hype or reality?

In 2014, the Global Initiative for Asthma (GINA) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) published a joint document on the asthma COPD overlap syndrome (ACOS). While the concept of ACOS is not new, it remains highly debated since its introduction in 1961. ACOS is characterized by persistent airflow limitation with features that are shared with both asthma and COPD. For example, younger asthmatics may develop persistent expiratory airflow limitation from airway remodeling or smoking.


DR. KHURANA

Alternatively, patients with COPD may have concurrent features of atopy. Prevalence of ACOS is estimated at 20% in those with obstructive airway disease (Gibson. *Thorax*. 2015;70[7]:683). Data from the COPDGene cohort suggest that patients with ACOS have more frequent and severe respiratory exacerbations, less emphysema, and greater airway wall thickness (Hardin. *Eur Respir J*. 2014;44[2]:341).

Studies evaluating differences in response to therapy are needed to make ACOS more relevant to the practicing clinician.

The mechanisms behind ACOS remain poorly understood. Gelb and colleagues recently reported their observations of loss of lung elastic recoil and presence of centrilobular emphysema in a subset of nonsmokers with chronic asthma and persistent expiratory airflow limitation (*Chest*. 2015; 148[2]:313; *J Allergy Clin Immunol*. 2015;136[3]:553). In two COPD cohorts, Christenson and colleagues found that asthma-associated gene signatures were associated with increased disease severity, eosinophil counts, bronchodilator reversibility, and ICS response (*Am J Respir Crit Care Med*. 2015;191[7]:758).

Data presented recently from Spiromics COPD and SARP severe asthma cohorts suggest that subjects with ACOS share a phenotype that falls between COPD and asthma. Allele frequency of candidate genes associated with smoking behavior and allergy in ACOS was intermediate between COPD and asthma (Li et al. *Am J Respir Crit Care Med*. 2016;A6237).

As with asthma and COPD, there exists significant heterogeneity within ACOS. Despite its high prevalence, evidence on how to consistently identify and best manage this group of patients is lacking. This is in part due to large clinical studies excluding patients with asthma COPD overlap. Additional research will help better understand the different phenotypes and endotypes of ACOS.

Real life pragmatic studies evaluating differences in response to therapy are needed to make ACOS more relevant to the practicing clinician.

Dr. Sandhya Khurana, FCCP
Vice-Chair

Clinical Research

Airway clearance therapies

Many acute and chronic respiratory conditions, such as pneumonia and bronchiectasis, are not only associated with an increase in the quantity and viscosity of respiratory secretions but also with impaired ciliary function and cough, with the latter being very common during mechanical ventilation and after strokes or thoracic surgical procedures. Retention of these secretions are associated with poor patient outcomes, and airway clearance therapies (ACT) are key to improving these outcomes and optimizing recovery after acute illnesses (Kim et. al. *Chest*. 2011;140[3]:626).


DR. AMALAKUHAN

Despite this knowledge, the study of simple ACTs has been largely overlooked for decades. Many of the treatments we currently use, such as positive expiratory pressure devices (for example, the Acapella device), percussive vests, and intrapulmonary percussive ventilation, have few studies to support their efficacy, with the ones that exist having very small sample sizes and show no superiority to simple manual techniques (Flume et al. *Respir Care*. 2009; 54[4]:522).

The study of simple ACTs has been largely overlooked for decades. Many of the treatments we currently use ... have few studies to support their efficacy.

As I walk by a patient's room and see a respiratory therapist clapping on a patient's back, I reflect on the fact that research on ACTs has essentially been at a standstill, and we continue to rely on therapies that are no better than the ones used in the 1800s.

Our institution has established an Airway Clearance Research Group and has already conducted several bench studies evaluating some of these airway clearance therapies, with goals to develop novel techniques and to start clinical trials, with collaboration from this research steering committee.

We hope that furthering the study of ACTs, and determining which therapies are most effective under different clinical settings, will not only improve clinical outcomes in chronic conditions such as bronchiectasis but also improve outcomes after pneumonia, strokes, thoracic surgeries, and during mechanical

Continued on page 51

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kenglebrecht@pcofmesa.com
Practice Manager
Office 480-835-7111 Ext 240

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Contact Joseph Rosman, MD
847 721 3817 or **rosj@sinai.org**

Pulmonary, Critical Care and Sleep Medicine in Southern Arizona

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* * * * * * * * * *

PASA is a sophisticated, well-established private group of six physicians and two nurse practitioners in Tucson, seeking a future partner.

Our practice includes both outpatient and inpatient services, including pulmonary, critical care, neurocritical care and sleep medicine. Our primary acute care hospital, Tucson Medical Center, is a major teaching facility for the University of Arizona, and our group is routinely involved in resident and medical student education.

We're seeking a dynamic and accomplished young physician with a passion for medicine, good interpersonal skills, a willingness to challenge herself/himself and us, and a desire to work collegially and collaboratively within a group.

Southern Arizona offers a wonderful environment for living and raising children, with ample theater, music, biking, hiking, climbing and even nearby skiing, along with the many resources of University of Arizona.

Come practice in a medically sophisticated community and live in a place where others come to vacation!

If interested, please fax a CV to (520) 382-2999 or contact us at **info@pasatucson.com**

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The Pulmonary • Critical Care • Sleep Medicine Specialists

PULMONARY / CRITICAL CARE / SLEEP MEDICINE – PORTLAND, MAINE

Chest Medicine Associates is a well-respected, established, 16 physician single specialty, private practice group in Portland, Maine. We seek pulmonary/critical care/sleep medicine physicians to expand our services. We have a strong partnership with Maine Medical Center, the state's largest tertiary care and teaching hospital, to provide 24/7 medical and neurological critical care and consultative pulmonary medicine services.

We offer a collegial and intellectually stimulating environment with opportunity for individual professional development. Our physicians are involved in active clinical research and extensively engaged in teaching in the Pulm-CCM fellowship, Medicine and Emergency Medicine residency programs. We have a robust outpatient practice with pulmonary function and sleep labs and in-office ultrasound. We provide regional expertise in pulmonary hypertension, cystic fibrosis, and lung cancer, and we offer endobronchial ultrasound and navigational bronchoscopy.

Enjoy life situated on Maine's southern coastline. The region is known for its excellent school systems, lifestyle, arts, exceptional culinary experiences, and abundant four season recreational opportunities in the nearby ocean, lakes, trails, and mountains.

Candidates must be BC/BE in pulmonary/critical care. Training, interest, and board certification in sleep medicine are highly desirable. Interest in programmatic development and clinical research in outpatient medicine (i.e. interstitial lung disease, airways diseases, sleep, etc) is welcome. A career focus in critical care or pulmonary/sleep medicine will be considered.

If interested, please e-mail cover letter and CV to
Stephen R. Gorman, DO at **sgorman@cmamaine.com**
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EOE

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Memorial Healthcare System is seeking an ACGME residency-trained, BE/BC thoracic surgeon to join two established general thoracic surgeons in its Division of Thoracic Surgery. The Division is the sole provider of thoracic surgical services to a large and diverse population and practices all aspects of thoracic surgery, including interventional endoscopy, with the exception of lung transplantation. Desirable candidates will possess expertise in minimally invasive surgery, including thoracoscopic, laparoscopic and robotic surgical techniques, and the ability to treat the full spectrum of pulmonary and esophageal diseases. A particular interest in esophageal surgery is desired as is expertise in POEM and EMR. Qualified candidates will also possess exceptional communication skills that will help expand the referral base, strengthen community ties and grow the esophageal surgery program. The Office of Human Research provides support for translational science research, including clinical trials, for those interested. This is a full-time, employed position with the multispecialty Memorial Physician Group. The position offers competitive benefits and a compensation package commensurate with training and experience. Professional malpractice and medical liability are covered under sovereign immunity.

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Current Practices and Future Directions in Pulmonary, Critical Care and Sleep Medicine: The 14th Year

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ventilation, where airway clearance is key. Something so simple has the potential to impact a wide population of patients.

Dr. Bravein Amalakuhan
Fellow-in-Training Member

Critical Care

Early mobilization of the critically ill patient

Deconditioning is a well known complication of prolonged ICU stays. It is a factor in long-term mechanical ventilation and contributes to an increased length of stay and comorbidities. The severity of illness, presence of invasive catheters, and the need for sedation in order to provide adequate ventilation are risk factors for immobility. Critically ill patients who are not mobilized experience a decreased quality of life (Needham. *JAMA*. 2008;300:1685).


DR. NARASIMHAN

The changes seen have been shown to persist up to a year after discharge, with a mean loss of 18% body weight, a 5% loss of muscle strength, and a decreased 6-minute walk distance (Herridge et al. *N Engl J Med*. 2003;348[8]:683; Herridge. *Crit Care Med*. 2009;37:S457).

There are many safety concerns when mobilizing critically ill patients, but studies have shown that early mobilization is safe with less than 1% of patients having adverse events such as falling, tube removal, and blood pressure instability (Bailey et al. *Crit Care Med*. 2007;35[1]:139). Barriers to mobilization include ICU staffing, deep sedation, ICU culture, and resources. Adherence to therapy is improved with the use of protocols.

These should include automated awakening trials and spontaneous breathing trials that allow for decreases in sedation and, therefore, improvement in mobilization performance (Drolet et al. *Phys Ther*. 2013;93[2]:197).

Decreases in ICU and hospital lengths of stay, time supported by mechanical ventilation, and cost reductions have been shown with mobilization.

Early mobilization improves mortality and decreases morbidity. Safe protocols to implement early mobilization have been developed around the country. Decreases in ICU and hospital lengths of stay, time supported by mechanical ventilation, and cost reduction have been shown with mobilization in multiple studies. A multidisciplinary team approach and a change in ICU culture will help to accomplish this important initiative.

Dr. Mangala Narasimhan, FCCP
Steering Committee Member

Home-Based Mechanical Ventilation and Neuromuscular Disease

Caregivers and training for kids receiving chronic home invasive ventilation

Despite years of experience in discharging pediatric patients receiving chronic home invasive ventilation, their mortality rate remains high, ranging from 21% to 27.5% with unscheduled readmission at 40% (Boroughs et al. *Home Health Nurse*. 2012;30:103) to 21% (Edwards et al. *J Pediatr*. 2010;157[6]:955; Kun et al. *Pediatr Pulmonol*. 2012:47[4]:409). While there were major improvements in technology and newer ventilators, and better community resources, the one key component of our HMV program remains the same – the caregivers. It is a frightening experience for every family to hear that their child needs ventilator support: every discharge is a daunting task and a life-changing experience.


MS. KUN

It seems logical to postulate that we might have improved mortality/readmission outcomes if we have competent caregivers.

Recent ATS guidelines recommend that "an awake, trained caregiver should be present at all times, and at least two family caregivers should be trained specifically for the child's care" (*Am J Respir Crit Care Med*. 2016;193[8]:e16).

The need to shore up on emergency care in the home is further supported when we review studies examining pediatric emergency home ventilation practices for both families and licensed home health nurses (Kun et al. *Pediatr Pulmonol*. 2010;45[3]:270; Kun. *Pediatr Pulmonol*. 2015;50[7]:691).

Understanding and responding to ventilator alarms remain a major challenge for caregivers and home health nurses. Future directions where we can help our caregivers and families improve home emergency care training include simulation video and using the technology of hand-held devices.

Sheila Kun, RN, BSN
Steering Committee Member

Interstitial and Diffuse Lung Disease

New clinic consortium offers help to patients with rare lung diseases

On the heels of the success of the LAM Foundation's research and clinic networks, several patient advocacy groups for rare lung diseases approached the LAM Foundation about incorporating the care of other rare lung diseases into the same clinic network.


DR. DILLING

In 2015, the Rare Lung Diseases Consortium was established. It represents a unique collaboration of these patient advocacy groups, the National Institutes of Health, and clinical investigators. It hopes to utilize the Rare Lung Disease Clinic Network as a resource in understanding the clinical course of several rare lung diseases and as a vehicle to initiate funded clinical trials in patients under the care of clinical investigators working at those various sites.

The first Rare Lung Diseases Consortium Conference is scheduled for September 22-25, 2016, in Cincinnati.

There are currently 29 geographically distributed Rare Lung Disease Clinic Network clinics in the United States, and another 18 clinics distributed internationally. The clinic directors have held two organizational meetings, including the most recent one in May 2016. The initial three research projects, "National Pulmonary Alveolar Proteinosis Registry," "A Longitudinal Study of Hermansky-Pudlak Syndrome," and "Multicenter International Durability and Safety of Sirolimus in LAM Trial (MIDAS)," are noninterventional longitudinal disease observational studies.

The first Rare Lung Diseases Consortium Conference is scheduled for September 22-25, 2016, in Cincinnati. It will be a combined educational and research conference, with attendance from clinicians, scientists, patient advocacy organizations, and patients with their families.

More information, including a list of the 22 diseases initially designated for care and study in the network and a map of all of the clinic network sites, is available at https://www.rarediseasesnetwork.org/cms/rld/.

Dr. Daniel F. Dilling, FCCP
Steering Committee Member

In Memoriam

CHEST has been informed of the following members' deaths. We extend our sincere condolences.

Vincent C. Manganiello, MD, PhD, died January 2016.

Lawrence H. Cohn, MD, FCCP – Past President, died January 9, 2016.

Suzanne K. Wedel, MD, FCCP, died March 2016.

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