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Regardless of exercise function, dyspnea, or lung function at baseline, all COPD patients improved after 20 or more days of pulmonary rehabilitation, based on a retrospective study.

All COPD patients benefitted from rehab

BY KATIE WAGNER LENNON
Frontline Medical News

Participation in at least 20 days of pulmonary rehabilitation by patients with chronic obstructive pulmonary disease (COPD) resulted in statistically significant improvements in quality of life, perception of health status, functional capacity, dyspnea, and depression, in a retrospective analysis.

Furthermore, improvements were seen regardless of the degree of exercise function, dyspnea, or lung function at baseline, reported lead investigator Praful Schroff.

Current American Thoracic Society and European Respiratory Society guidelines recommend the consideration of pulmonary rehabilitation for patients who have persistent symptoms and activity limitations and for those who are unable to adjust to their illness despite optimal medical management (Am J Respir Critical Care Med. 2013 Oct 15;188[8]:e13-64). Recent research had shown that pulmonary rehabilitation benefits patients with COPD without regard to their level of baseline dyspnea, but the influence of the level of baseline exercise capacity on the benefits of pulmonary rehabilitation had not been

See **Pulmonary rehab** • *page 6*

Men with COPD and sarcopenia at high risk for osteopenia

Fat-free mass loss linked to BMD loss

BY DEEPAK CHITNIS
Frontline Medical News

FROM CHEST

Men experiencing sarcopenia who also have been diagnosed with chronic obstructive pulmonary disease (COPD) are at a significantly higher risk of developing osteopenia and osteoporosis than are men who do not suffer from COPD, according to a new study published in Chest.

"Muscle depletion has been considered a risk factor for low [bone mineral density (BMD)] in the healthy general population [but] data on the association between sarcopenia and osteopenia/osteoporosis in COPD patients are lacking," wrote the investigators of the study, coauthored by Moo Suk Park, MD, of Yonsei University in Seoul, South Korea (Chest. 2017 Jan. doi: 10.1016/j.chest.2016.12.006).

"Although previous studies showed that loss of fat-free mass (FFM) was related to BMD loss in COPD patients, it is difficult to know the genuine relationship between skeletal muscle mass and BMD because whole body FFM contains a large proportion of water-retaining organs and nonmuscle soft tissue," the authors wrote.

The investigators examined data from the Korean National Health and Nu-

See **Osteopenia** • *page 4*

INSIDE

Joint guidelines address TB diagnosis

BY MARY ANN MOON
Frontline Medical News

A clinical practice guideline for diagnosing pulmonary, extrapulmonary, and latent tuberculosis in adults and children has been released jointly by the American Thoracic Society, the Centers for Disease Control and Prevention, and the Infectious Diseases Society of America.

The American Academy of Pediatrics also provided input to the guideline, which includes 23 evidence-based recommendations. The document is intended to assist clinicians in high-resource countries with a low incidence of TB disease and latent TB infection, such as the United States, said David M. Lewinsohn, MD, PhD, and his associates on the joint task force that wrote the guideline.

There were 9,412 cases of TB disease reported in the United States in 2014, the most recent year for which data are available. This translates to a rate of

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ATS=American Thoracic Society; ERS=European Respiratory Society; JRS=Japanese Respiratory Society; ALAT=Latin American Thoracic Association; %FVC=percent predicted forced vital capacity.

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

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

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

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

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

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

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

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

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

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

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

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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.

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Sarcopenia in COPD

Osteopenia *from page 1*

tritional Examination Survey (KNHANES), looking for men at least 20 years of age with COPD who had both pulmonary function test and the dual-energy x-ray absorptiometry (DXA) performed on them during the years 2008-2011. A total of 864 men were deemed eligible for inclusion, and were scored for sarcopenia and osteopenia/osteoporosis; the former was assessed via the appendicular skeletal mass index (ASMI), with the latter done via T score.

"Sarcopenia and presarcopenia were defined according to the presence of ASMI values that were less than two standard deviations (SDs) and between 2SDs and 1SD, respectively, below the mean value of a young male reference group aged 20-39 years," according to the investigators. "Osteoporosis, osteopenia, and normal BMD were identified according to the lowest T-score of the three measured locations and were defined according to the World Health Organization criteria."

Results showed that sarcopenia in men with COPD led to a higher risk

of having low BMD, with an odds ratio of 2.31 (95% confidence interval, 1.53-3.46; *P* less than .001). A higher percentage of men categorized as having presarcopenia had low BMD (157/445, 35.53%), compared to just 15.4% (15/332) of those with normal BMD (*P* less than .001). Similarly, while only 1.2% (4/332) of those with sarcopenia had normal BMD, 8.3% (37/445) had low BMD (*P* = .017). The ASMI to T-score ratio of 0.408 (*P* less than .001) indicated a significant association between appendicular skeletal muscle mass and BMD.

"This study reminds us that we need to consider these other issues in a COPD patient's care, since the outcomes from these problems … can be devastating," Dr. Gartman said.

"This study affirms the systemic nature of COPD, as it is not merely a disease that manifests as breathlessness and other respiratory complaints, but affects many aspects of a patient's functionality and overall health," explained Eric J. Gartman, MD, of Brown University, Providence, R.I. "In clinical practice, this study reminds us that we need to consider these other issues in a COPD patient's care, since the outcomes from these problems (e.g. hip fractures) can be devastating."

DR. GARTMAN

Echoing those thoughts in a separate interview, Vera De Palo, MD, FCCP, of Signature Healthcare in Brockton, Mass., said this study will help health care providers "deepen our understanding of these associations and contributing factors, [and] it may lead to targeted interventions that help to slow the sarcopenia that contributes to the dysfunction and fragility in our patients."

DR. DE PALO

A critical limitation of this study, however, is the sample population, according to Dr. Gartman. "It is solely made up of Korean men, thus somewhat limiting the generalizability to a larger population [and] especially to women, given that there are several other considerations surrounding effects on BMD."

No funding sources were disclosed. The authors reported no conflicts.

dchitnis@frontlinemedcom.com

6MWD scores rose significantly

Pulmonary rehab *from page 1*

systematically studied, wrote Mr. Schroff, the designer of the analysis and a student in the division of pulmonary, allergy, and critical care medicine at the University of Alabama, Birmingham (UAB).

The analysis focused on 229 COPD patients enrolled in the pulmonary rehabilitation program at UAB during 1996-2013, all of whom completed questionnaires both at enrollment and after completion of their respective exercise programs. The mean forced expiratory volume in 1 second (FEV_1) percent predicted for the cohort was 46.3%. The researchers used pulmonary function data from tests performed within 2 years of enrollment. Change in quality of life and perception of health status were measured using the 36-item Short Form Health Survey (SF-36), dyspnea was assessed using the San Diego Shortness of Breath Questionnaire (SOBQ), depression was assessed using the Beck Depression Inventory (BDI)-II, and functional capacity was assessed using the 6-minute-walk-distance (6MWD) test.

Patients benefited from participating in pulmonary rehabilitation "independent of their underlying functional capacity," the researchers noted.

On average, the patients reported clinically significant improvements in most components of the SF-36, including an 11.5-unit, a 16.4-U, and a 12.4-U increase in physical function, social function, and vitality, respectively (*P* less than .001 for all three). The patients also experienced clinically important improvements in the 6MWD test (increase of 52.4 m; *P* less than .001) and dyspnea (decrease of 9.1 U in the SOBQ; *P* less than .001). On average, patients' depression decreased by 3 U, using the BDI II (*P* less than .001).

When patients in this study were divided into groups based on various aspects of their health at baseline, the levels of improvements seen by each group in most components of the SF-36, the 6MWD, the SOBQ, and the BDI-II were almost always similar.

"We add to the literature by comparing outcomes across quartiles of baseline exercise capacity and showing that patients benefit independent of underlying functional capacity," said Mr. Schroff and his colleagues.

A few differences in the outcomes following pulmonary rehabilitation were observed between these baseline characteristics–based groups. When patients were grouped by exercise capacity, for example, those with the lowest baseline exercise capacity (as measured by the 6MWD) experienced the largest incremental improvement in the 6MWD. Additionally, when patients were grouped by dyspnea score, those with the worst baseline dyspnea experienced the greatest reduction in dyspnea. However, those with the lowest lung function made the smallest improvement in the 6MWD. Another of these differences was observed between the patients with the lowest baseline lung function and the patients in the other lung function-based quartiles. Those with the worst lung function made the smallest improvement in the 6MWD, which was 39.0 m, on average. All of these subgroups achieved clinically significant improvements in the 6MWD and SOBQ (Ann Am Thorac Soc. 2017 Jan 1;14[1]:26-32).

Each exercise session included aerobic exercises, resistance training, and breathing techniques. Cardiovascular exercise was prescribed starting at 20-30 minutes of continuous or interval bouts and was gradually increased until 30-45 minutes of exercise was achieved. Patients also received education sessions lasting 40-60 minutes on understanding their disease, smoking cessation counsel-

Continued on following page

VIEW ON THE NEWS

Vera A. De Palo, MD, FCCP, comments: The care goals for COPD patients often include efforts to improve functionality. The authors of this retrospective analysis of pulmonary rehabilitation for patients with persistent symptoms and activity limitations report significant patient-reported improvements in physical function, social function, and vitality. Dyspnea and the patients' reported level of depression also improved. Participation in pulmonary rehab may help our COPD patients better modulate the quality of life impact of their disease.

IN THIS ISSUE

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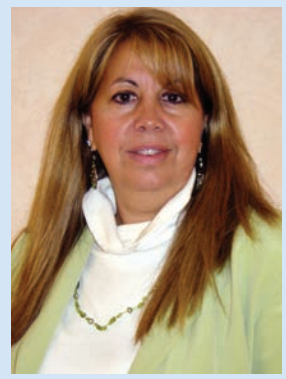

Vera A. De Palo, MD, MBA, FCCP, is Medical Editor in Chief of CHEST Physician.

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USPSTF punts on sleep apnea screening

BY MARY ANN MOON
Frontline Medical News

The U.S. Preventive Services Task Force neither supports nor rejects screening asymptomatic adults for obstructive sleep apnea in the primary-care setting, because the current evidence is inadequate to assess the benefits and harms of doing so, according to a Recommendation Statement published online Jan. 23 in JAMA.

The USPSTF makes recommendations about the effectiveness of specific health care services for patients who don't have related signs or symptoms. In this case, the Recommendation Statement addresses adults who don't snore excessively; gasp or choke while sleeping; or report the daytime sleepiness, impaired cognition, or mood changes typically associated with obstructive sleep apnea, said Kirsten Bobbins-Domingo, PhD, MD, chair of the organization and lead author of the Recommendation Statement, and her associates (JAMA. 2017 Jan 23. doi: 10.1001/jama.2016.20325).

The USPSTF commissioned a comprehensive review of the literature to examine whether screening such patients by primary caregivers would effectively identify those who have obstructive sleep apnea and lead to treatment that would prevent the elevated rates of death, cognitive impairment, motor vehicle crashes, cardiovascular events, and cerebrovascular events related to the disorder. Daniel E. Jonas, MD, of the University of North Carolina at Chapel Hill and his associates reviewed 110 relevant studies involving 46,188 participants.

They found that the accuracy and clinical utility of numerous OSA screening tools was uncertain. In particular, the Epworth Sleepiness Scale, the STOP (Snoring, Tiredness, Observed Apnea, and High Blood Pressure) questionnaire, the STOP-BANG (STOP plus BMI, Age, Neck Circumference, and Gender) questionnaire, the Berlin Questionnaire, the Wisconsin Sleep Questionnaire, and the Multivariable Apnea Prediction (MVAP) tool have not been adequately validated in primary care settings.

Moreover, no studies directly assessed whether screening had an impact on actual health outcomes. Several treatments, notably continuous positive airway pressure and mandibular advancement devices, did improve intermediate outcomes such as scores on the apnea-hypopnea index, scores on the Epworth Sleepiness Scale, and blood pressure levels, but the evidence did not show that this in turn improved mortality, cardiovascular events, or the other "hard" outcomes of interest, Dr. Jonas and his associates said in their Evidence Report (JAMA. 2017 Jan 23. doi: 10.1001/jama.2016.19635).

VIEW ON THE NEWS

Don't misinterpret the USPSTF recommendation

This recommendation must not be misinterpreted. If clinicians are discouraged from directly questioning patients about apnea signs and symptoms or from using short screening questionnaires to identify those at high risk for the disorder, it would negatively influence public health.

Primary care clinicians have an important role in mitigating the adverse health consequences of obstructive sleep apnea, which can stem from years of unrecognized disease.

Susan Redline, MD, is at the Sleep Health Institute and in the Division of Sleep and Circadian Disorders at Brigham and Women's Hospital and Harvard Medical School and Beth Israel Deaconess Medical Center, all in Boston. She reported ties to Jazz Pharmaceuticals, RosMed, and the Beckman Company, as well as serving on the American Academy of Sleep Medicine's board of directors. Dr. Redline made these remarks in an editorial accompanying the USPSTF reports (JAMA. 2017;317:368-70).

Continued from previous page

ing, appropriate use of inhalers, diet and nutrition, and stress management. Subjects with other concurrent chronic respiratory diseases were excluded from the analysis.

The researchers noted that their findings may not be generalizable to patients with disease burdens causing them to drop out of the study. "Although we have previously shown that baseline levels of dyspnea, FEV_1, and exercise capacity did not influence dropout rates, this could be a source of bias," they noted.

"Patients with COPD experienced meaningful improvements in quality of life, dyspnea, exercise capacity, and depression, regardless of baseline lung function, dyspnea, and exercise capacity. Current guidelines should be amended to recommend pulmonary rehabilitation to all patients with COPD, regardless of their baseline level of disease burden," the analysis' authors said.

Three of the study's authors reported receiving grants and other fees or a single grant from various sources. The other authors, including Mr. Schroff, said they had nothing to disclose.

klennon@frontlinemedcom.com

11 million in U.S. may have TB

Tuberculosis *from page 1*

3.0 cases per 100,000 persons. Two-thirds of the cases in the United States developed in foreign-born persons. "The rate of disease was 13.4 times higher in foreign-born persons than in U.S.-born individuals (15.3 vs. 1.1 per 100,000, respectively)," wrote Dr. Lewinsohn of pulmonary and critical care medicine, Oregon Health & Science University, Portland, and his colleagues.

Even though the case rate is relatively low in the United States and has declined in recent years, "an estimated 11 million persons are infected with *Mycobacterium tuberculosis*. Thus … there remains a large reservoir of individuals who are infected. Without the application of improved diagnosis and effective treatment for latent [disease], new cases of TB will develop from within this group," they noted (Clin Infect Dis. 2016 Dec 8;64[2]:e1-33. doi: 10.1093/cid/ciw694).

Among the guidelines' strongest recommendations:

- Acid-fast bacilli smear microscopy should be performed in all patients suspected of having pulmonary TB, using at least three sputum samples. A sputum volume of at least 3 mL is needed, but 5-10 mL would be better.
- Both liquid and solid mycobacterial cultures should be performed on every specimen from patients suspected of having TB disease, rather than either type alone.
- A diagnostic nucleic acid amplification test should be performed on the initial specimen from patients suspected of having pulmonary TB.
- Rapid molecular drug susceptibility testing of respiratory specimens is advised for certain patients, with a focus on testing for rifampin susceptibility with or without isoniazid.
- Patients suspected of having extrapulmonary TB also should have mycobacterial cultures performed on all specimens.
- For all mycobacterial cultures that are positive for TB, a culture isolate should be submitted for genotyping to a regional genotyping laboratory.
- For patients aged 5 and older who are suspected of having latent TB infection, an interferon-gamma release assay (IGRA) is advised rather than a tuberculin skin test, especially if the patient is not likely to return to have the test result read. A tuberculin skin test is an acceptable alternative if IGRA is not available, is too expensive, or is too burdensome.

The guideline also addresses bronchoscopic sampling, cell counts, and chemistries from fluid specimens collected from sites suspected of harboring extrapulmonary TB (such as pleural, cerebrospinal, ascetic, or joint fluids), and measurement of adenosine deaminase levels.

VIEW ON THE NEWS

Vera A. De Palo, MD, FCCP, comments: *Mycobacterium tuberculosis* is a leading cause of morbidity and mortality globally, impacting the public health. Timely diagnosis for the initiation of treatment is important.

This work was supported by the American Thoracic Society, the Centers for Disease Control and Prevention, and the Infectious Diseases Society of America, with input from the American Academy of Pediatrics. Dr. Lewinsohn reported having no relevant financial disclosures; his associates reported ties to numerous industry sources.

Score guides screening for cancer in VTE patients

BY MARY ANN MOON
Frontline Medical News

FROM CHEST

A newly devised risk score may help identify which patients with acute venous thromboembolism (VTE) are most likely to have occult cancer and where they are likely to have it, according to a report published online in CHEST.

Although VTE is known to occur before an occult cancer becomes symptomatic in a minority of patients, clinicians don't agree on which patients with VTE should be screened for occult cancer or on how extensive that screening should be. Some favor a basic screening with only a clinical history, physical exam, simple lab tests, and a chest x-ray, while others advocate a more thorough work-up to improve the patient's chance for a cure.

"The potential benefits and harms of such screening are controversial, partly because there is little evidence" concerning which patients are at highest risk and which cancer types/sites should be assessed, said Luis Jara-Palomares, MD, PhD, of the medical surgical unit of respiratory diseases, Virgen del Rocio Hospital, Seville, Spain, and his associates.

Dr. Jara-Palomares and his associates devised a prognostic score by assigning points to the variables they found to be most significantly associated with occult cancer.

For example, male sex was accorded 1 point, chronic lung disease or a high platelet count was accorded 1 point, age over 70 years or anemia was accorded 2 points, and postoperative or prior VTE was accorded negative 2 points. The incidence of occult cancer was significantly lower among patients whose total score was 2 points or less (5.8%) than among those whose total score was 3 points or higher (12%).

The mean age of these study participants was 63 years, and approximately half were women. A total of 444 (7.6%) were diagnosed as having cancer at 1-24 months after presenting with VTE. Most of these cancers were discovered within 6 months of the VTE.

Patients who had occult cancer were significantly more likely than those who did not to be male and older than 70 years of age; to have chronic lung disease, an elevated platelet count, and/or anemia; and to have a history of recent surgery and/or prior VTE.

The percentage of VTE patients who had occult cancer increased with advancing age, from 2%-3% in the youngest age group (younger than 50 years) to 8%-12% in the oldest age group (older than 70 years). Among men with occult cancer, the most frequently affected sites were the lung (26%), prostate (17%), and colon/rectum (10%). Among women, the most frequent types of cancer were colorectal (19%), breast (12%), uterine (9.1%), hematologic (8.6%), pancreatic (7.6%), and stomach (6.6%).

Overall, more than half of the men who had occult cancer had cancer affecting the lung, prostate, or colon/rectum, while two-thirds of the women who had occult cancer had

cancer affecting the colon/rectum, breast, or abdomen. "This is important because [cancer] screening is not necessary in all VTE patients, but any information suggesting [which] patients are at increased risk and [which] sites are more common may be of help to decide the most appropriate work-up for each patient," the investigators noted.

To determine which patients are most likely to have occult cancer and which cancer types are most likely to develop, the investigators analyzed data from RIETE (the Computerized Registry of Patients With Venous Thromboembolism), an international registry of more than 50,000 consecutive patients with confirmed acute VTE. They focused on 5,863 patients who presented with pulmonary embolism (34%), deep vein thrombosis (48%), or both disorders (18%) and were followed for at least 2 years for the development of cancer.

The accuracy of this risk scoring system must be tested further in a large validation cohort before it can be widely adopted. If it proves to be accurate, then patients with low total risk scores could forgo the expense, discomfort, and psychological stress of extensive cancer screening, Dr. Jara-Palomares and his associates said.

Continued on following page

Continued from previous page

Men whose total score is 3 points or more could benefit from a rectal exam and fecal occult blood test to rule out colorectal cancer, a rectal exam and prostate-specific antigen test to rule out prostate cancer, and a chest CT to rule out lung cancer.

"[Cancer] screening is not necessary in all VTE patients, but any information suggesting [which] patients are at increased risk and [which] sites are more common may be of help to decide the most appropriate work-up for each patient."

Women whose total score is 3 points or higher could benefit from a fecal occult blood test to rule out colorectal cancer, a mammogram to rule out breast cancer, and abdominopelvic CT to rule out uterine, pancreatic, and stomach cancer, they noted.

The RIETE Registry is supported by an unrestricted educational grant from Sanofi Spain and by Bayer Pharma AG. Dr. Jara-Palomares reported having no relevant financial disclosures; his associates reported ties to Sanofi, Bayer, and LEO Pharma.

Evaluate non-PV triggers in AF with sleep apnea

BY TED BOSWORTH
Frontline Medical News

ORLANDO – Patients with atrial fibrillation (AF) should be screened for obstructive sleep apnea (OSA), because this information may be useful in guiding ablation strategies, according to results of a prospective study.

The study, which associated OSA in AF with a high relative rate of non–pulmonary vein (PV) triggers, has contributed to the "growing body of evidence implicating sleep apnea in atrial remodeling and promotion of the AF substrate," Elad Anter, MD, associate director of the clinical electrophysiology laboratory at Beth Israel Deaconess Medical Center, Boston, reported at the annual International AF Symposium.

Despite the close association between OSA and AF, it has been unclear whether OSA is a causative factor. Dr. Anter suggested that mechanistic association is strengthening, however.

It has been hypothesized that OSA generates AF substrate through negative intrathoracic pressure changes and autonomic nervous system activation. But Dr. Anter reported that there is more recent and compelling evidence that the repetitive occlusions produced by OSA result in remodeling of the atria, producing scar tissue that slows conduction and produces susceptibility to reentry AF.

A newly completed prospective multicenter study adds support to this hypothesis. In the protocol, patients with paroxysmal AF scheduled for ablation were required to undergo a sleep study, an AF mapping study, and follow-up for at least 12 months. A known history of OSA was an exclusion criterion. For the effect of OSA to be seen in isolation, there were exclusions for other major etiologies for AF, such as heart failure or coronary artery disease.

The AF mapping was conducted when patients were in sinus rhythm "to evaluate the baseline atrial substrate and avoid measurements related to acute electrical remodeling," Dr. Anter explained.

Of 172 patients initially enrolled, 133 completed the sleep study, 118 completed the mapping study, and 110 completed both and were followed for at least 12 months. Of these, 43 patients without OSA were compared with 43 patients with OSA defined as an apnea-hypopnea index (AHI) of at least 15. Patients in the two groups did not differ significantly for relevant characteristics, such as body mass index, age, presence of hypertension, or duration of AF; but the left atrial (LA) volume was significantly greater ($P = .01$) in those with OSA than in those without.

Even though the prevalence of voltage abnormalities was higher in the OSA group for the right ($P = .01$) and left atria ($P = .0001$) before ablation, the prevalence of PV triggers (63% vs. 65%), non-PV triggers (19% vs. 12%), and noninducible triggers (19% vs. 23%) were similar.

After ablation, PV triggers were no longer inducible in either group, but there was a striking difference in inducible non-PV triggers. While only 11.6% remained inducible in the

non-OSA group, 41.8% ($P = .003$) remained inducible in the OSA patients.

"AF triggers in OSA were most commonly located at the LA septum, at the zone of low voltage and abnormal electrograms, as determined during sinus rhythm," Dr. Anter reported. "Ablation of these triggers at the zone of tissue abnormality in the OSA patients resulted in termination of AF in 9 (64.2%) of the 14 patients."

Overall, at the end of 12 months, 79% of those without OSA remained in arrhythmia-free survival, versus 65.1% of the group with OSA that were treated with PV isolation alone.

The lower rate of success in the OSA group highlights the importance of specifically directing ablation to the areas of low voltage and slow conduction in the left anterior septum that Dr. Anter indicated otherwise would be missed.

"These zones are a common source of extra-PV triggers and localized circuits or rotors of AF in OSA patients," he reported. "Ablation of these low voltage zones is associated with improved clinical outcome in OSA patients with paroxysmal AF."

The data, which Dr. Anter said are consistent with a growing body of work regarding the relationship of OSA and AF, provided the basis for suggesting that AF patients undergo routine screening for OSA.

In patients with OSA, ablation of PV triggers alone even in paroxysmal AF "may not be sufficient," he cautioned. "Evaluation of non-PV triggers should also be performed."

Dr. Anter reported financial relationships with Biosense Webster and Boston Scientific.

VIEW ON THE NEWS

Jason M. Lazar, MD, FCCP, comments: Atrial fibrillation (AF) is the most common cardiac arrhythmia encountered in clinical practice and is associated with increased morbidity and mortality due to thromboembolism, stroke, and worsening of pre-existing heart failure. Both its incidence and prevalence are increasing as AF risk increases with advancing age.[1] While the strategies of heart rate control and anticoagulation to lower stroke risk and rhythm control have been found comparable with regard to survival, many patients remain highly symptomatic because of palpitations and reduced cardiac output.[1]

Structural abnormalities of the atria, including fibrosis and dilation, accompanied by conduction abnormalities, provide the underlying substrate for AF. It is well established that AF episodes perpetuate atrial remodeling leading to more frequent and prolonged AF episodes. Hence, there is the long-standing notion that "AF begets AF." While a variety of antiarrhythmic drugs have been employed over the years to prevent AF recurrences and to maintain sinus rhythm, their use has decreased over the past 2 decades due to their major side effects and their potential of proarrhythmia.

Catheter-based ablation techniques have gained widespread acceptance for the prevention of AF recurrences and the maintenance of sinus rhythm. Since the junction between the pulmonary veins and the left atrium has long been appreciated as a contributer to AF initiation and/or perpetuation, catheter-based radiofrequency ablation directed at the junction of the pulmonary veins and left atrium has become the mainstay of nonpharmacologic treatment of AF.[2] The efficacy of this technique has been found comparable if not superior to antiarrhythmic drug therapy.[2] Recently, the use of a cryoablation technique, which produces a large and more homogeneous lesion, has been tested and found comparable to radiofrequency ablation in terms of safety and efficacy.[3] Despite considerable improvement in the understanding and application of catheter-based ablation, published technical success rates have ranged from 51%-77% and are likely considerably lower in "real world" practice.[4] Therefore there is strong need and opportunity for technical refinement.

Since AF patients represent a heterogeneous group of patients with CV diseases of varying type and severity as well as comorbidities, it stands to reason that the pulmonary venous–left atrial junction may not be the sole culprit region of all cases of AF and that other anatomical locations might serve as triggers for AF.

In support of this notion are the results of the prospective multicenter study presented by Dr. Elad Anter at the annual International AF Symposium. This important study is consistent with and expands upon prior studies that have suggested that sites within the atria remote from the pulmonary veins may serve as triggers for AF, rather than lower technical success of pulmonary vein ablation.[5] It further highlights the importance of fibrosis and associated electrical dispersion to the pathogenesis of AF.[6] However, the recommendation that patients with AF be screened for OSA is not new, as nearly half of patients with AF also have OSA.[7] While AF and OSA share common risk factors/comorbidities such as male gender, obesity, hypertension, coronary artery disease, and congestive heart failure, OSA has been found to be an independent risk factor for AF development.

It is important to know whether OSA was treated, as the presence of OSA raises the risk of AF recurrence and OSA treatment decreases AF recurrence after ablation.[8,9] Conversely, in the setting of OSA, AF is more resistive to rhythm control. Enhanced vagal activation, elevated sympathetic tone, and oxidative stresses due to oxygen desaturation and left atrial distension have all been implicated in the pathogenesis linking OSA to the development of AF. Repeated increases in upper airway resistance during airway obstruction have been shown to lead to atrial stretch, dilation, and fibrosis.[10] Since patients with heart failure, coronary artery disease, and other underlying causes for AF were excluded from the onset, the results may not be applicable to a large segment of AF patients. Exclusion of underlying cardiac conditions potentially raised the yield of patients found to have OSA and the potential value of OSA screening. Of note: Less than half of patients that were enrolled had complete data for analysis, which may further limit applicability of the study findings. All patients had paroxysmal AF and were in sinus rhythm while the mapping procedure was performed, leaving questions as to how to approach patients presenting acutely with persistent or long standing AF, or those recently treated with antiarrhythmic therapy. Also, since arrhythmia-free survival decreases from 1 to 5 years after AF ablation, and short-time success rates do not predict longer success rates, the present study results should be interpreted with cautious optimism.[11]

However, these limitations should not detract from the major implications of the study. In the setting of AF, OSA should be clinically suspected not only because of the frequent coexistence of the two disorders but because the presence of OSA should prompt electrophysiologists to consider non–pulmonary vein triggers of AF prior to ablation attempts. The consideration of alternative ablation sites might help to explain the lack of ablation procedure endpoints to predict long-term success of ablation and holds promise for increasing technical success rates. Given that airway obstruction may occur in other clinical settings such as seizure-induced laryngospasm and that seizures may induce arrhythmias and sudden death, there is potential for non–pulmonary vein sites to trigger AF and other arrhythmias in settings other than OSA as well.[12]

This study underscores the notion that with regard to AF ablation, "no one site fits all" and "clinical mapping" may serve as a valuable adjunct to anatomical mapping.

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Three-biomarker assay helps to distinguish viral from bacterial lower respiratory tract infections

BY DEEPAK CHITNIS
Frontline Medical News

An assay designed to distinguish between bacterial and viral infections of the lower respiratory tract appears effective and shows promise for helping hospital physicians reduce overprescribing of antibiotics to children, a study showed.

"It is often not possible to differentiate between bacterial and nonbacterial disease on the basis of clinical judgment alone, [so] antibiotics are prescribed almost twice as often as required in children with acute respiratory tract infections in the USA," wrote Chantal B. van Houten, of the University Medical Centre Utrecht (the Netherlands), and associates in a study published in Lancet Infectious Diseases.

The assay in question is called ImmunoXpert, which uses three biomarkers – tumor necrosis factor–related apoptosis-inducing ligand (TRAIL), interferon-gamma–induced protein-10 (IP-10), and C-reactive protein (CRP) – to determine if a lower respiratory tract infection has a viral or bacterial origin. A total of 777 subjects, aged 2-60 months, were recruited from four hospitals in the Netherlands and two hospitals in Israel between October 16, 2013, and March 1, 2015 (Lancet Inf Dis. 2016 Dec. doi: 10.1016/S1473-3099(16)30519-9).

The patients all had fevers with unidentified sources when they presented, and had a follow-up assessment carried out 28 days after baseline. Blood samples and nasal swabs were collected within 24 hours of presentation for assay analysis. Additionally, every subject was diagnosed as "bacterial" or "viral" by a three-member panel of pediatricians, whose diagnoses were based on the data available from the follow-up assessment and from clinical and laboratory data. The panel diagnosis for each subject was used as the reference standard.

Of the 777 subjects initially recruited, 200 were excluded from the final analysis for various reasons. Of the 577 who remained, the panel diagnosed 435 as having a viral infection and 71 as having a bacterial infection; 71 were deemed "inconclusive." The panel was unanimous in 354 of these cases, and a majority of the panel (two of the three experts) agreed in 443 of these cases. In unanimous cases, the sensitivity of distinguishing between viral and bacterial cases correctly was 87.8%, with a specificity of 93.0%. The panel's positive and negative predictive value were 62.1% and 98.3%, respectively.

The assay's sensitivity rate in distinguishing between viral and bacterial infections was very close: 86.7%, with a specificity of 91.1%, which the authors noted was "promising diagnostic accuracy." The positive predictive value of the assay was 60.5%, while the negative predictive value was found to be 97.8%.

Regarding the 71 cases that were deemed "inconclusive," Dr. van Houten and coauthors acknowledged that "such inconclusive cases are inherent to studies without a gold standard, and this was taken into account when calculating the sample size." Additionally, they noted that follow-up studies should take into consideration the costs of utilizing assay testing like ImmunoXpert, in order to better assess the financial implications that adopting the technology would have on a health care facility.

Nevertheless, the investigators concluded, "our findings [support] the need for implementation research to examine the added clinical utility of ImmunoXpert to diagnose bacterial infection in clinical care for children with lower respiratory tract infection and fever without source presenting at the hospital."

Funding for this study was provided by MeMed Diagnostics. Dr. van Houten and coauthors did not report any relevant financial disclosures.

dchitnis@frontlinemedcom.com

VIEW ON THE NEWS

Study results are promising, but come with caveats

The combined measurement of CRP, TRAIL, and IP-10 distinguished bacterial from viral infections with a sensitivity of 86.7% and a specificity of 91.1%. The combined assay is significantly more effective than procalcitonin determinations for identifying the cause of infection, as it improves the diagnostic classification of bacterial infections by 6.3% and of viral infections by 5.4%.

In comparison with CRP alone, the combined assay is similarly effective for classifying bacterial cases; however, the combined assay does improve the identification of patients with viral infections by 8.6%.

Nevertheless, the combined assay has several limitations and is not yet ready for routine use in clinical practice. The test requires advanced laboratory techniques and cannot be used outside hospitals.

Beyond that limitation, the study itself had some shortcomings. The results came from a relatively small number of children, none of whom had an underlying disease that might modify host response to infection. Additionally – as in the case of all of the studies that have tried to differentiate bacterial and viral infection – the definition of cause of infection varies. Finally, respiratory infections are frequently classified on the basis of clinical and radiological findings, and the results of a microbiological assessment of nasopharyngeal swabs.

"However, it is well known that the investigation into upper respiratory secretions in children can be confounding and lead to the erroneous classification of a lower respiratory disease, and that bacteria and viruses can simply be carried and could have no association with the cause of a disease. This means that future studies should confirm the results of host protein-based assays in larger study populations with various characteristics, and consider their cost to benefit ratios in relation to their real effect on reducing antibiotic use."

Susanna Esposito, MD, and Nicola Principi, MD, are with the University of Milan. Their opinions are excerpted from a commentary on the article by Dr. van Houten et al. (Lancet Inf Dis. 2016 Dec. doi: 10.1016/S1473-3099(16)30536-9). They had no relevant financial disclosures.

Childhood PCV program produces overall protection

BY RANDY DOTINGA
Frontline Medical News

The findings raise questions about "the merit of offering [the 13-valent pneumococcal vaccine] in older groups" in places that have a children's PCV program, the researchers noted.

Childhood pneumococcal conjugate vaccines continue to indirectly produce widespread societal protection against invasive pneumococcal disease, a review and meta-analysis showed.

In fact, the reviewed studies suggest that the use of these vaccines in children can lead to an overall 90% drop in invasive pneumococcal disease within fewer than 10 years.

Herd immunity appears to be at work, the review authors said. The effect is so powerful that the findings raise questions about "the merit of offering [the 13-valent pneumococcal vaccine] in older groups" in places that have a children's pneumococcal conjugate vaccine (PCV) program, Tinevimbo Shiri, PhD, of the University of Warwick, Coventry, England, and colleagues said in a meta-analysis of 242 studies published in the January issue of Lancet Global Health (2017 Jan;5[1]:e51-9).

U.S. guidelines recommend vaccinations for older people, although

Continued on following page

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the recommendations are up for review in 2018.

The authors wrote that childhood PCVs have had a tremendous impact since a seven-valent version (PCV7) of the vaccine was first released in 2000. "In vaccinated young children, disease due to serotypes included in the vaccines has been reduced to negligible levels."

But unvaccinated people, especially the elderly, remain susceptible.

The meta-analysis is an update of a 2013 systematic review (Vaccine. 2013 Dec 17;32[1]:133-45). For the updated review, which included 70 studies from the previous review, the researchers focused on studies from 1994 to 2016 that examined the effects of introducing PCVs in children.

Most of the studies were done in North America (42%) and Europe (38%); 4% were performed in poor or middle-income countries.

The researchers found that "[herd] immunity effects continued to accumulate over time and reduced disease due to PCV7 serotypes, for which follow-up data have generally been available for the longest period, with a 90% average reduction after about 9 years."

Specifically, the review estimated it would take 8.9 years for a 90% reduction in invasive pneumococcal disease for grouped serotypes in the PCV7 and 9.5 years for the extra six grouped serotypes in the 13-valent PCV. The latter vaccine was introduced in 2010.

The 11 serotypes contained in PPV23 but not in PCV13 "did not change invasive pneumococcal disease at any age," according to the researchers.

The researchers found evidence of a similar annual reduction in disease linked to grouped serotypes in the 23-valent pneumococcal polysaccharide vaccine in adults aged 19 and up. They noted that the 11 serotypes contained in PPV23 but not in PCV13 "did not change invasive pneumococcal disease at any age."

In countries with mature pediatric PCV programs, including Cana-

VIEW ON THE NEWS

PCVs' effectiveness hampered

The impact of pneumococcal conjugate vaccines has been hampered by serotypes that they don't address.

Data from this meta-analysis have shown an overall reduction of invasive pneumococcal disease in all unvaccinated age groups of just 1%. New extended-valency vaccines will be required to halt this erosion of PCV impact.

David Goldblatt, PhD, MBChB, of the Great Ormond Street Institute of Child Health and University College London, made these remarks in a commentary accompanying the review and meta-analysis (Lancet Glob Health. 2017 Jan;5[1]:e6-7). Dr. Goldblatt reported receiving grants and personal fees from GlaxoSmithKline, Merck, Sharpe, and Dohme and a publication with Pfizer.

da, Germany, the Netherlands, the U.K., and the United States, invasive pneumococcal disease due to PCV7 serotypes has been nearly eliminated through indirect protection; i.e., the average incidence of PCV7-invasive pneumococcal disease after nearly a decade of PCV7 use is less than 10 per 100,000 people. In these countries, consistent decreases in vaccine-type adult community-acquired pneumonia (CAP) or meningitis, and nonbacteraemic CAP, have been observed, indicating substantial indirect protection effects against noninvasive disease from childhood vaccination."

The review authors noted that a major "evidence gap" exists in the effectiveness of childhood PCV programs in low-income countries.

"Because these countries are increasingly undertaking childhood vaccination programs, research to assess the indirect effects in these settings is particularly relevant," they wrote.

The review's limitations include the possibility that the results could be thrown off by variations across nations in areas like diagnostic protocols, surveillance, and outcome measures.

The authors of the review, funded by the Policy Research Program of England's Department of Health, reported no relevant financial disclosures.

‘Asthma pathway’ sped treatment, cut ED transfers

BY LUCAS FRANKI
Frontline Medical News

Partnerships between community emergency departments and pediatric tertiary care centers are feasible and can improve care of pediatric asthma, according to Theresa A. Walls, MD, of the Children’s National Health Systems, Washington, D.C., and her associates.

A total of 724 asthma patients aged 2-17 years were included in the study, which was published in Pediatrics (2016. doi: 10.1542/peds.2016-0088). Of this group, 289 (40%) were treated at a community ED before a pediatric tertiary care center intervention, an evidence-based pediatric “asthma pathway” in a community ED, and 435 (60%) were treated after that intervention. The pathway provides decision support for caring for asthma patients in a form that is familiar to community ED staff and uses change concepts of standardization, development of operational definitions, and moving steps in a process closer together. “A key component of the pathway is documentation of an asthma score, which provides standardization and an operational definition for providers,” the researchers wrote.

They incorporated the pathway into electronic health records, splitting the pathway into a triage order set and a provider order set. They also met with staff in the community ED to educate them about the evidence supporting the pathway.

Treatment with steroids was significantly increased post intervention, with 76% of patients receiving steroids compared with 60% of patients before the intervention. Time to start of steroids was significantly reduced after the intervention, falling from 196 minutes to 105 minutes. No significant difference was seen in the number of returns to the ED, but the number of transfers fell from 14% before the intervention to 10% after the intervention. “Because the overwhelming majority of pediatric emergency visits occur in community EDs, partnerships with these EDs can broaden the impact of quality improvement activities and should be part of future quality improvement efforts,” the investigators concluded.

lfranki@frontlinemedcom.com

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: Dr. Walls and her group developed a quality improvement (QI) initiative with a community emergency department. One important part of the study was the use of an asthma score, which helped determine steps for ED therapy. They found great results in the large number of study patients who were treated for asthma acutely at the community ED after the QI project was implemented. It would be great if the next step in the collaboration would be education for when to start inhaled steroids on patients with persistent asthma to decrease emergency room utilization!

Quality improvement project cut COPD readmissions

BY M. ALEXANDER OTTO
Frontline Medical News

AT CHEST 2016

LOS ANGELES – With a handful of common-sense steps, the Kaiser Permanente Los Angeles Medical Center reduced 30-day hospital readmissions for chronic obstructive pulmonary disease (COPD) from 17.4/1,000 in December 2013 to 11.9/1,000 in December 2015.

The 57 readmissions avoided in 2015 saved the medical center $700,359, according to a report at the annual meeting of the American College of Chest Physicians.

"[It's] cheaper for us to go this way than to wait for readmissions.," said Augusto Cam, a respiratory therapist and COPD case manager, one of the project members.

The quality improvement project started in 2013 after staff realized their COPD readmission rates were significantly higher than other area hospitals, and likely to increase.

Mr. Cam and his colleagues discovered several problems. "Leaving the hospital, [COPD patients] didn't know what medication was for what, or their medication schedule. They didn't know how to use their inhalers, and didn't understand what the disease process was all about, and what it was doing to them," he said.

ALEXANDER OTTO/FRONTLINE MEDICAL NEWS

Augusto Cam (left) and Dr. Luis Moreta-Sainz reported that education, consults, and rehab cut readmissions.

There was little continuity of care after discharge; many patients didn't even have a pulmonologist. Essentially, COPD patients were lost to follow-up until they returned to the emergency department with another exacerbation.

A rapid Plan, Do, Study, Act cycle was the first step; it identified solutions that would work based on COPD management guidelines and published studies.

The team staggered their changes over 2 years. Pulmonary consults for acute exacerbation admissions shot up, and respiratory therapists started to stop by to educate almost every COPD patient about medication use, trigger avoidance, and other matters. Patients began watching educational videos from their bed.

Changes were made after discharge, too. "We felt strongly that pulmonary rehabilitation needed to be an integral part of care, and that patients had to be connected to the pulmonary clinic," said pulmonologist, Luis Moreta-Sainz, MD.

Patients were booked for a pulmonologist at the clinic soon after they left the hospital, and greeted there by their COPD navigator – a respiratory therapist operating at the top of their license – who bridged the gap between inpatient and outpatient care and oversaw their case, helping with medical, psychosocial, and palliative needs. Patients were also channeled into pulmonary rehab, three sessions per week for 6-8 weeks, with additional sessions as needed. The outpatient education emphasized and expanded the inpatient lessons, and patients exercised on treadmills and other equipment. They learned how to use resistance bands at home to increase upper body strength and decrease disability. Kaiser increased the number of weekly pulmonary rehab slots from 8 to 64 to make it happen. After rehab, patients were offered a pedometer to measure how many steps they walked, and a phone number to report it each day. Those who participated got a call from the navigator when they fell below targets.

The work was funded by Kaiser; Dr. Moreta-Sainz and Mr. Cam have no disclosures.

aotto@frontlinemedcom.com

VIEW ON THE NEWS

Daniel Ouellette, MD, FCCP, comments: On a recent morning, two of my scheduled clinic patients were "no-shows." Both of them were patients with COPD that I had recently cared for in-hospital for an exacerbation. While I know that snow may have played a role, there are other barriers to care, including lack of access to transportation, poor health literacy, and no effective health insurance. I am increasingly recognizing that neuropsychiatric issues affect my COPD patients' wellness. The Kaiser team's system-based approach to reducing COPD admissions looks to be the path along which we should all travel.

COPD spirometry use suboptimal in primary care

BY M. ALEXANDER OTTO
Frontline Medical News

AT CHEST 2016

LOS ANGELES – Spirometry is the standard for diagnosing chronic obstructive pulmonary disease, but it's underused and misused in primary care, according to investigators from the Corpus Christi (Tex.) Medical Center.

The conclusion is based on a review of 65 patients from internal medicine and family practice clinics near the medical center, but "I do think this [pattern] is representative of what we are seeing in every primary care office. This has been a problem [documented] in the literature for a decade, and it remains a problem," said lead investigator Stephen Eikermann, DO, an internal medicine resident at the center.

Only 29% of patients diagnosed with chronic obstructive pulmonary disease (COPD) at the two clinics had spirometry. Patients "are being diagnosed based on symptoms," and those with atypical symptoms are probably being missed, he said.

Meanwhile, of those diagnosed by spirometry, 32% didn't meet the gold-standard Global Initiative for Chronic Obstructive Lung Disease (GOLD) diagnostic criteria by having a postbronchodilator forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) of less than 70%. "People who have asthma are being tagged as having COPD," and once that diagnosis is in the chart, it's hard to remove, even when patients improve. "With the COPD readmission penalty in place, an erroneous diagnosis of COPD [has] significant financial risks," Dr. Eikermann said.

Patients are being diagnosed based on symptoms. Those with atypical symptoms are probably being missed.

DR. EIKERMANN

The guidelines state that COPD should be considered in any patient who has dyspnea, chronic cough, or sputum production, plus smoking or other risks. "Spirometry is required to make the diagnosis."

Dr. Eikermann and his colleagues are planning lectures and a quick reference handout to remind people about the guidelines. They also plan to remind practitioners that Medicare pays at a reasonable rate for spirometry.

aotto@frontlinemedcom.com

PULMONARY PERSPECTIVES: High levels of air pollution in Delhi and adverse health effects

BY G.C. KHILNANI, MD, FCCP; AND PAWAN TIWARI, MD, DM

"Nature's condition, rightly interpreted, reveals a society's culture and traditions as directly as does a novel or a newspaper or a code of laws."
–Roderick F. Nash

Adverse effects of air pollution on human health have been known ever since the "Great London Smog" in 1952. Mankind is paying for rapid industrialization by adversely affecting the air that we breathe. The developed world has been able to improve the environmental standards by following stringent norms and practices regarding engines, fuels, and industrial safety. However, the same cannot be said about developing countries. Delhi, the capital of India, has seen high levels of air pollution for the last several decades.


DR. KHILNANI


DR. TIWARI

The number of registered vehicles in Delhi has doubled over the last 10 years. This, along with rapidly increasing numbers of small scale industries and inconsistently regulated construction work, has led to ever-increasing levels of air pollution in Delhi. The city has witnessed smog for the last few years.

Smog causing disruption of daily life and health hazards has been reported from Los Angeles, Beijing, and many other major cities around the world. The London Smog of 1952 caused approximately 4,000 deaths within 4 days (Davis D, et al. *Environ Health Perspectives*. 2002;110[12]:A734) and caused another 8,000 deaths over next few weeks to months (Bell ML, et al. *Environ Health Perspectives*. 2004;112[1]:6).

Common sources and pollutants with reference to Delhi

As in most cities around the world, rapid industrialization and increases in vehicles using fossil fuels are important contributors to ambient air pollution in Delhi. Additional sources of air pollution unique to Delhi include dust generation during building construction, ash generation from thermal power plants, crop residue burning in neighboring states, and burning of fossil fuels for domestic, as well as small scale, industrial use. Major pollutants include particulate matter (both PM2.5 and PM10), nitrogen oxides (NOx), carbon monoxide (CO), sulfur dioxide (SO2), and ozone (O3).

Delhi is distinct in its geographic location adjoining the Great Indian Desert (Thar) in the west and cool hilly regions in the north and east. This accounts for great seasonal variations in temperature, humidity, and wind speed. Also, being a landlocked territory, there are no moderating effects of sea breeze available to other metropolitan cities (like Mumbai and Chennai).

Dust storms during the summer from the neighboring state of Rajasthan cause an increase in suspended particulate matter (SPM). All these contribute to seasonal and climatic variations in air quality. In addition, the use of fire crackers during the festival of Diwali leads to dangerous levels of air pollution also.

Adverse health effects as witnessed in clinics and community

Many adults, without any prior history of respiratory illness, attended our outpatient department (OPD) with breathlessness, chest congestion, and wheezing requiring inhaled bronchodilators. A significant proportion of patients with previously diagnosed respiratory diseases (including COPD, bronchial asthma, or interstitial lung disease) reported to OPDs or emergency services with worsening cough, wheezing, and breathlessness. A few patients coming from outside Delhi for routine follow-up had exacerbation of COPD after coming to Delhi (personal observations).

We have previously reported increases in asthma, COPD, and acute coronary events (by 21.30%, 24.90%, and 24.30%, respectively) due to higher than acceptable levels of air pollutants in Delhi (Pande JN, et al. *Indian J Chest Dis Allied Sci*. 2002;44[1]:13). Another concerning development has been the increase in the number of persons being diagnosed with bronchial asthma in middle age, probably related to worsening air quality. Persons at extremes of age (young children and elderly) are particularly affected.

Studies in Delhi assessing ambient air pollution–related morbidity and mortality

Studies have used risk of mortality/morbidity due to air pollution model (Ri–MAP) to assess health impact of various air pollutants in Delhi. According to their estimates, there were 18,229 excess deaths in Delhi in the year 2010, more than 50% of which were due to cardiovascular or respiratory causes. Also, 26,525 excess hospital admissions due to COPD exacerbation could be attributed to ambient air pollution (Nagpure A, et al. *Atmospheric Pollution Res*. 2014;5[3]:1309).

Interventions: Work in progress

The Central Pollution Control Board convened an Expert Committee (Dr. Khilnani as a member) for formulation and implementation of Air Quality Index (AQI) in major Indian cities (http://cpcb.nic.in/FINAL-REPORT_AQI_.pdf).

Currently reported AQI is calculated by using the following parameters: sulfur dioxide (SO_2), nitrogen dioxide (NO_2), particulate matter (PM10,PM2.5) averaged over 24 hours, along with ozone (O3) and carbon monoxide (CO), averaged over 1-8 hours. AQI is classified as good (0-50), satisfactory (51-100), moderate (101-200), poor (201-300), very poor (301-400), and severe (greater than 401).

AQI is reported daily in leading newspapers along with public and private news channels. Thanks to the mainstream and social media, smog has become a commonly understood word. Air pollution is a hot topic of discussion among people of all socioeconomic and demographic strata.

Children of almost all schools in Delhi pledged not to use firecrackers this Diwali. People are increasingly sharing taxis or carpooling. Utilization of public transport is gradually increasing.

The Delhi government ordered temporarily shutting off the only working thermal power plant in the megacity (source of 10%-15% of ambient air pollution). The government is also working on an action plan based on air quality, which includes both preventive and prohibitive measures.

A significant proportion of patients with previously diagnosed respiratory diseases reported to outpatient departments or emergency services with worsening cough, wheezing, and breathlessness.

Delhi Transport Corporation operates one of the world's largest fleets of compressed natural gas–operated buses. Delhi Metro Corporation has been lauded by the United Nations for its efforts in reducing the carbon footprint and air pollution.

Yet, a lot needs to be done to improve the air quality in Delhi. Last mile connectivity remains a big hurdle; improving this will go a long way in promoting use of public transport. Implementation of methods to reduce particulate matter generation at construction sites, promoting use of vehicles using electricity or compressed natural gas, increasing parking charges for vehicles, banning the use of diesel-driven heavy vehicles in the city, road cleaning with vacuum cleaners to reduce PM 10 generation, increasing green areas, and promoting carpooling or taxi sharing are some other initiatives that need to be implemented on priority. Delhi and surrounding states need to strengthen awareness drives and norms to discourage crop residue burning on a priority basis.

Conclusion

Delhi's poor air quality during this winter has indeed affected the respiratory health of the population. Healthy people, as well as those with preexisting respiratory diseases, are adversely affected. A series of actions at the personal and institutional level is required to control this menace.

Dr. Khilnani is Professor, and Dr. Tiwari is Research Officer, Department of Pulmonary Medicine & Sleep Disorders, All India Institute of Medical Sciences, New Delhi, India.

Asthma ruled out in 33% of diagnosed adults

BY MARY ANN MOON
Frontline Medical News

Asthma was ruled out in 33% of adults in the general Canadian population who had been diagnosed by a physician during the preceding 5 years, according to a report published in JAMA.

In a prospective multicenter cohort study involving 613 asthma patients, 203 had no evidence of current asthma when they underwent serial assessments of respiratory symptoms, lung function, and bronchial provocation testing while not taking asthma medications. More than 90% of these 203 participants safely refrained from using the medications for an additional 1-year follow-up period, said Shawn D. Aaron, MD, of Ottawa Hospital Research Institute, and his associates in the Canadian Respiratory Research Network.

Some of these patients were likely misdiagnosed initially and some likely experienced remission since their initial diagnosis.

To assess whether some patients could safely discontinue asthma medications because they no longer had the disease, the researchers performed a random sampling of the general adult population (approximately 17,000 people) living in urban, suburban, or rural areas in and around the 10 largest cities in Canada during a 3-year period. Those who reported that a member of the household had been diagnosed as having asthma within the previous 5 years were invited to participate in the study (JAMA. 2017;317[3]:269-79).

A total of 613 men and women (mean age, 51 years) completed the

Continued on following page

VIEW ON THE NEWS

Revisiting asthma diagnoses important

"The study by Aaron [et al.] is an important reminder that in addition to reviewing asthma symptoms and treatment, trying to understand if the diagnosis is still appropriate is an important part of clinical care."

The study gives clinicians two insights: First, adults diagnosed as having asthma may not continue to have the disease years later, or at least may not require treatment indefinitely. And second, physiological testing is an essential component of diagnosis and will help avoid unnecessary treatment and missed alternative causes for signs and symptoms.

Helen M. Hollingsworth, MD, and George T. O'Connor, MD, are at the Pulmonary Center at Boston University. Dr. O'Connor is an associate editor of JAMA. He reported serving as a consultant for AstraZeneca and receiving grants from Janssen Pharmaceuticals. Dr. Hollingsworth and Dr. O'Connor made these remarks in an editorial accompanying Dr. Aaron's report (JAMA. 2017;317[3]:262-3).

Continued from previous page

study, undergoing spirometry to assess airflow obstruction, methacholine challenges to assess airway hyperresponsiveness, clinical examination by a pulmonologist, and, if indicated, tapering and discontinuation of asthma medications. Those in whom asthma was ruled out were closely followed for 1 year, undergoing repeat bronchial challenge testing and reporting any worsening of asthma signs and symptoms.

At baseline, 87% of the participants said that they had recently used asthma medications and 45% said they used such medications daily. The remainder had already stopped using asthma medications, an indication that many patients can tell when their asthma has remitted (or was never present) and may adjust their medication use with or without a physician's guidance, Dr. Aaron and his associates said.

Current asthma was confirmed in 62.3% of the study participants. The primary study outcome – the proportion of patients in whom a current asthma diagnosis was ruled out – was 33.1%, or 203 patients. Only 44% of these participants who did not have current asthma had undergone objective testing before their initial diagnosis, compared with 56% of patients in

whom asthma was confirmed. This indicates that "whenever possible, physicians should order objective tests, such as prebronchodilator and postbronchodilator spirometry, serial peak flow measurements, or bronchial challenge tests, to confirm asthma at the time of initial diagnosis," the investigators said.

A total of 35% of the participants in whom asthma was ruled out had been using daily asthma medications. "Use of asthma medications in these patients presumably provided only risks for medication adverse effects and cost, with little opportunity for therapeutic benefit," the researchers noted. Twelve patients were found to have serious cardiorespiratory conditions that had been misdiagnosed as asthma.

During the additional year of follow-up, 22 of the 203 patients in whom asthma had been ruled out had a positive bronchial challenge test result at 6 or 12 months. Six resumed using asthma medications and one was treated with a brief course of oral corticosteroid.

The Canadian Institutes of Health Research supported the study. Methapharm provided provocholine and Trudell Medical International provided the peak flow meters used in the study. Dr. Aaron made no relevant financial disclosures; his associates disclosed ties to numerous industry sources.

Delayed and early chemo yield similar outcomes

BY NEIL OSTERWEIL
Frontline Medical News

Patients with non–small cell lung cancer (NSCLC) for whom adjuvant chemotherapy must be delayed for as long as 18 weeks have mortality outcomes that are no worse than those of patients who start chemotherapy soon after surgery, and those who undergo delayed chemotherapy have a significantly lower risk for death than patients who have no chemotherapy at all, investigators report.

A retrospective review of data on 12,473 patients with previously untreated NSCLC showed that there were no significant differences in 5-year overall survival (OS) estimates among patients who started multiagent chemotherapy at 18-38 days postoperatively, from 39 to 56 days after surgery (the reference interval),

or from 57 to 127 days after surgery, reported Daniel J. Boffa, MD, of Yale University, New Haven, Conn., and his colleagues.

In addition, when they used propensity score matching to pair patients who received chemotherapy with patients who did not undergo chemotherapy, they found that even late chemotherapy was associated with a significantly lower risk for death.

There were no significant differences in 5-year overall survival estimates among patients who started multi-agent chemotherapy at 18-38 days postoperatively, from 39 to 56 days after surgery, or from 57 to 127 days after surgery.

"Clinicians should still consider chemotherapy in appropriately selected patients that are healthy enough to tolerate it, up to 4 months after NSCLC resection. Further study is warranted to confirm these findings," the investigators concluded (JAMA Oncol. 2017 Jan 5. doi: 10.1001/jamaoncol.2016.5829).

In the retrospective review of re-

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cords from the National Cancer Database, the investigators limited the study to patients for whom chemotherapy is typically prescribed: those with lymph node metastases, tumors 4 cm or larger, and/or local extension of disease. They looked at the association between the time to initiation of adjuvant chemotherapy and survival using Cox modeling with restricted cubic splines, a validated statistical method for evaluating links between survival and independent variables.

Dr. Boffa and his associates found that the unadjusted Kaplan-Meier 5-year OS estimates did not differ between the groups, at 53% for the early chemotherapy group (hazard ratio vs. the reference group, 1.009; $P = .79$), 55% for the reference group, and 53% for the later chemotherapy group (HR, 1.037; $P = .27$).

Clinicians should consider chemo in appropriately selected patients up to 4 months after NSCLC resection.

DR. BOFFA

Comparing adjuvant chemotherapy timing on the efficacy of surgery alone in patients matched by tumor stage and other features, the researchers found that chemotherapy started during any of the three intervals was associated with an approximately 34% reduction in risk of death compared with no chemotherapy (HR for the respective time intervals, 0.672, 0.645, and 0.664; P less than .001 for each comparison).

The study helps to clarify for clinicians the benefits of adjuvant chemotherapy in select patients with NSCLC in a real-world setting, Howard (Jack) West, MD, of the Swedish Cancer Institute, Seattle, said in an accompanying editorial (JAMA Oncol. 2017 Jan 5. doi: 10.1001/jamaoncol.2016.5798).

"While retrospective data cannot define the benefit of delayed adjuvant chemotherapy with the clarity of a prospective randomized trial, we must remember that in the land of the blind, the one-eyed man is king; these limited data inject an evidence-based answer for a very common clinical question for which we have been forced by necessity to rely only on our best judgments," he wrote.

The study was internally supported. The authors and Dr. West reported no conflict of interest disclosures.

VIEW ON THE NEWS

M. Patricia Rivera, MD, FCCP, comments: This retrospective study provides clinically relevant information for providers evaluating patients after surgical resection who meet criteria for adjuvant chemotherapy but may not be ready to receive it 8 weeks after surgery (considered optimal time). The study echoes the results of an earlier retrospective population-based study (Booth et al. Cancer. 2013;119:1243-50) of 1,032 patients that found a delay in start of chemotherapy (greater than 10 weeks) occurred in 35% of cases and was not associated with inferior survival. The findings that late chemotherapy is better than no adjuvant therapy is also very important.

Comorbidities drive mortality for 2.5 years post op

BY RICHARD MARK KIRKNER
Frontline Medical News

After older patients undergo lung resection for stage I non–small cell lung cancer, they are actually at greater risk of death from something other than lung cancer for up to 2.5 years, according to researchers at Memorial Sloan-Kettering Cancer Center, New York. The findings were published online in the Journal of Clinical Oncology (2016;34. doi: 10.1200/JCO.2016.69.0834).

"As age increases, the risk of competing events increases, such as death from noncancer diseases," wrote Takashi Eguchi, MD, and coauthors. "In this era of personalized cancer therapy, important to the stratification of individualized treatments is the determination of how both cancer and noncancer risk factors – specifically, comorbidities associated with increasing age – contribute to the risk of death."

The researchers examined outcomes in three different age groups: younger than 65, 65-74, and 75 and older. The study focused on 2,186 patients with pathologic stage I non–small cell lung cancer (NSCLC) among a population of 5,371 consecutive patients who had resection for primary lung cancer from 2000 to 2011. Seventy percent of patients in the study group were 65 and older, and 29.2% were 75 and older.

In all age groups, the calculated 5-year cumulative incidence of death (CID) for lung cancer–specific causes exceeded that for noncancer causes, but at significant intervals the 65-and-over groups were more likely to die from the latter. For the overall study group, noncancer-specific causes accounted for a higher CID through 18 months after surgery, when the CID for both cancer and noncancer causes crossed at around 2.9. At 5 years, the overall lung cancer–specific CID was 10.4 vs. 5.3 for noncancer-specific causes.

However, in the older age groups, those trends were more pronounced. In those aged 65-74, CID for both causes met at around 3.15 at 18 months (10.7 for lung cancer–specific and 4.9 for noncancer specific at 5

Continued on following page

VIEW ON THE NEWS

M. Patricia Rivera, MD, FCCP, comments: This study highlights the importance of accurately assessing for comorbidites, especially in the older lung cancer patient in order to best determine treatment options. Results of this study also reiterate the importance of patient selection, thoughtful discussion and shared decision making in lung cancer screening, particularly in patients with significant comorbid conditions who are in the upper end of the screening age range.

Several PD-L1 levels tests have high concordance

BY MITCHEL L. ZOLER
Frontline Medical News

VIENNA – Several different tests for PD-L1 levels in tumor cells of patients with metastatic non–small cell lung cancer showed high concordance when run at seven French centers, boosting confidence in the clinical utility of this testing to guide first-line pembrolizumab treatment of patients with this cancer.

Among 27 laboratory-developed tests for PD-L1 (programmed death–ligand 1) levels in tumor cells that used any one of three prespecified testing platforms (made by Dako, Ventana, or Leica), 14 (52%) had "similar" concordance when compared with reference assays, Julien Adam, MD, said at the World Conference on Lung Cancer, sponsored by the International Association for the Study of Lung Cancer.

"These results will provide the basis for making national recommendations for PD-L1 testing in patients with non–small cell lung cancer [NSCLC]" in France, added Dr. Adam, a pathologist at Gustave Roussy Cancer Center in Paris. "We expect to produce recommendations by the second half of 2017."

Several single-center studies had examined harmonization of several different PD-L1 tests, but the new, multicenter study examined several different antibodies and platforms systematically, he noted.

Although the results came entirely from French centers, the results will also likely influence U.S. practice, predicted Shirish M. Gadgeel, MD, a thoracic oncologist at the Karmanos Cancer Institute in Detroit. The approval pembrolizumab (Keytruda) received from the Food and Drug Administration in October specified that patients with metastatic NSCLC had to show PD-L1 expression in the tumor using a FDA-approved test to receive pembrolizumab as first-line treatment. "Before pembrolizumab's approval there was no incentive to do PD-L1 testing," but now it is becoming routine, he said.

mzoler@frontlinemedcom.com
On Twitter @mitchelzoler

VIEW ON THE NEWS

NSCLC treatment needs PD-L1 test harmonization

Researchers have developed several different antibodies for measuring levels of PD-L1 in tumor cells and the antibodies can be used in several different testing platforms. Although most laboratories focus on using one specific immunohistochemical platform, the overall status of real-world PD-L1 testing is messy.

In the results reported by Dr. Adam, concordance weighted kappa coefficients of 0.8 or higher show extremely good concordance, and coefficients of 0.6-0.79 show good concordance. Several of the tests and testing sites reported by Dr. Adam showed concordance coefficients within these ranges. In certain other cases the concordance coefficients were very low, which prompts concern about the reliability of these low-scoring tests. The results show that the results you see in one laboratory with a specific antibody and platform test may not always remain consistent with the same antibody and platform used elsewhere.

Testing for PD-L1 is important because right now it is how we identify patients with metastatic non–small cell lung cancer who are candidates for first-line pembrolizumab treatment. Knowing how individual laboratories perform PD-L1 testing and having confidence in the results is very important for managing these patients. We need to understand what individual laboratories do and what their results mean. A close collaboration between clinicians and pathologists is needed to optimize patient care.

Michael Boyer, MD, is a professor of medicine at the University of Sydney and a thoracic oncologist and chief clinical officer of the Chris O'Brien Lifehouse in Sydney. He has received research support from Merck and from AstraZeneca, Bristol-Myers Squibb, Clovis, Eli Lilly, Pfizer, and Roche. He made these comments as designated discussant for the report.

Continued from previous page

years), whereas for those 75 and older, CID for noncancer causes exceeded that for lung cancer–related causes for 2.5 years, when both were around 6; reaching 13.2 for lung cancer–specific and 9 for noncancer specific at 5 years.

In the 65-and-younger group, lung cancer– and noncancer-specific CIDs were equal for about 3 months after surgery, when the lung cancer deaths tracked upward and the trends diverged (at 5 years, CID was 7.5 for lung cancer–specific and 1 for noncancer specific).

"We have shown that in patients with stage I NSCLC, the majority of postoperative severe morbidity, 1-year mortality, and 5-year noncancer-specific mortality were attributable to cardiorespiratory diseases," Dr. Eguchi and colleagues said.

"We have also shown that short-term mortality is primarily attributable to noncancer-specific diseases." The findings underscore the importance of screening older patients for noncancer-specific diseases that could alter outcomes, the researchers said.

Of the 2,186 stage I NSCLC patients in the study, 167 developed severe morbidities after surgery; 68.3% developed respiratory problems and 18.6% went on to develop cardiovascular problems. Patients who had lobectomy were more likely to develop respiratory problems than were those who had sublobar resection, Dr. Eguchi and coauthors said.

Respiratory and cardiovascular diseases were the most frequent causes of death early after surgery. At 30 days, respiratory disease accounted for 5 deaths and cardiovascular disease 7 of 15 total deaths at 30 days; and at 90 days, 11 and 7, respectively, of 27 overall deaths. Even at 1 year, noncancer issues were the leading cause of death (50%), followed by lung cancer–specific causes (27.8%) and other cancer specific disease (13.3%).

"Noncancer-specific mortality represents a significant competing event for lung cancer–specific mortality, with an increasing impact as age increases," Dr. Eguchi and coauthors said. "These findings can provide patients with more accurate information on survivorship on the basis of their individual preoperative status and help determine patients' optimal treatment options."

The study received financial support from coauthor Prasad S. Adusumilli, MD. Dr. Eguchi and the other coauthors had no relevant financial relationships to disclose.

Macrolide resistance on rise in *S pneumoniae*

BY KATIE WAGNER LENNON
Frontline Medical News

The incidence of *Streptococcus pneumoniae* resistance to the macrolide azithromycin – one of the most commonly prescribed antibiotics for treating pneumonia – was almost 50% in 2014, according to a report by Kara Keedy, PhD, executive director of microbiology at Cempra Pharmaceuticals, and her colleagues.

The researchers prospectively collected and investigated 4,567 nonreplicative community-acquired bacterial pneumonia (CABP) *S pneumoniae* isolates between 2008 and 2014 in the United States, according to the report presented as a poster at IDWeek 2016. The isolates were tested for susceptibility by broth microdilution methods, according to Clinical and Laboratory Standards Institute breakpoint criteria. Macrolide resistance rates were based on azithromycin and/or clarithromycin minimal inhibitory concentrations as available, with only data on azithromycin having been collected in 2014.

On average in 2014, 48.4% of isolates were resistant to azithromycin and 31.3% of isolates exhibited high-level resistance to the macrolide, while 12.6% of isolates were co-resistant to macrolide and penicillin.

The overall resistance of *S pneumoniae* to azithromycin exceeded 30% in all of the nine geographical divisions of the Centers for Disease Control and Prevention (CDC), with the high-level resistance of this bacterial cause of CABP to azithromycin having been greater than 25% in eight of the CDC divisions.

The co-resistance of *S pneumoniae* to azithromycin and penicillin was highest in the CDC's East South Central division in 2014. The regions with the largest percentages of isolates with high-level macrolide resistance were the East South Central (43.2%), the West South Central (38.1%), and the Mid-Atlantic (35.0%). The regions with the largest percentages of overall macrolide resistance were the West South Central (62.9%), the East South Central (56.8%), and the South Atlantic (53.2%).

The researchers concluded that *S pneumoniae* is the most common bacterial cause of CABP and that antibiotic resistance to it is "a significant clinical challenge."

The analysis also determined that the 2014 overall rate of macrolide resistance in *S pneumoniae* in the United States of 48.4% is higher than it was for any of the four earlier years examined. In 2008, 2009, 2010, and 2011, those macrolide resistance rates were 39.7%, 40.2%, 37.1%, and 44.3%, respectively.

The researchers concluded that *S pneumoniae* is the most common bacterial cause of CABP and that antibiotic resistance to it is "a significant clinical challenge as highlighted by" the CDC having listed it as a threatening pathogen in the urgent category. Dr. Keedy and her associates noted that in the United States, macrolides, amoxicillin/clavulanate, and respiratory fluoroquinolones are the most frequent agents prescribed to treat almost all community-acquired respiratory infections.

"Macrolide resistance in *S pneumoniae* is continuing to increase in the U.S.," the researchers reported in the poster. "Both low- and high-level macrolide resistance have been reported to cause clinical failures and other negative outcomes including longer hospital stays and higher costs."

The study also examined the abilities of several other drugs, including the fourth-generation macrolide solithromycin, to inhibit *S pneumoniae* isolates. Solithromycin does not yet have approved Clinical and Laboratory Standards Institute breakpoints, so only minimum inhibitory concentrations (MICs) were presented.

According to the study, more than 50% of *S pneumoniae* isolates were inhibited by 0.008 mcg/mL solithromycin. Additionally, solithromycin had one of the lowest MICs against *S pneumoniae* of all of the drugs tested in the study. The higher end of the MICs against *S pneumoniae* for solithromycin and moxifloxacin was 0.25, which was lower than the higher end of the MICs for any of the other drugs tested against *S pneumoniae* isolates.

Solithromycin is the first fluoroketolide in phase III clinical development. It "shows activity against all macrolide-resistant strains of *S pneumoniae* isolates, irrespective of the location in the U.S.," according to the poster.

The data included in the poster were extracted from a global study by JMI Laboratories. Cempra funded this study. Dr. Keedy and the other authors of the poster are employees of Cempra.

klennon@frontlinemedcom.com

VIEW ON THE NEWS

Daniel Ouellette, MD, FCCP, comments: "Mrs. Jones told me over the phone that she was having another COPD exacerbation. I called her pharmacy and ordered five days of azithromycin," the fellow said.

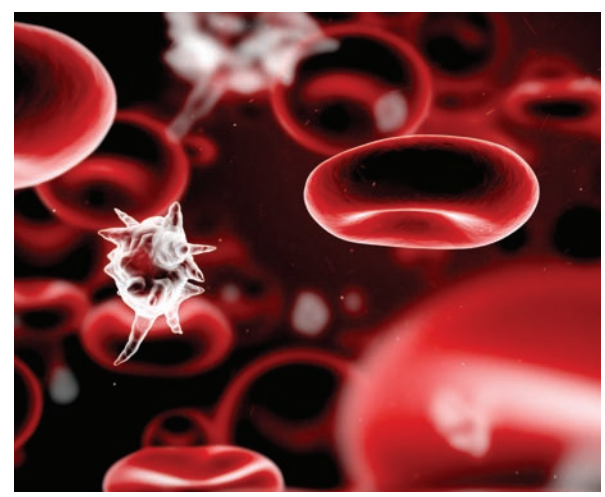
How many of us have heard that line? How many of us have done that ourselves? Did you do that today? Dr. Keedy and her colleagues report that in all geographic areas in the US, resistance to azithromycin for *S pneumoniae* now exceeds 30%. On average, 48.4% of *S pneumoniae* isolates display resistance in the US. Without antibiotic stewardship by all of us, azithromycin, along with other antibiotics, will become an expensive placebo.

SOFA score may be best to identify sepsis in the ICU

BY DOUG BRUNK
Frontline Medical News

Among critically ill patients admitted to the ICU with a suspected infection, defining sepsis by an increase of 2 or more points in the Sequential Organ Failure Assessment score yielded greater prognostic accuracy for in-hospital mortality, compared with the quick SOFA and the systemic inflammatory response syndrome criteria, results from a large analysis showed.

"Accurate diagnostic criteria and consensus definitions have an important role in adult intensive care medicine, providing tools for research, benchmarking, performance monitoring, and accreditation," researchers from The Australian and New Zealand Intensive Care Society Centre for Outcomes and Resource Evaluation reported in the Jan. 17, 2017, edition of JAMA. "Seymour and colleagues published data concerning the validity of a 2 or more–point change in the Sequential [Sepsis-Related] Organ Failure Assessment (SOFA) score as a means of identifying sepsis among patients who are critically ill with suspected infection, assuming a SOFA of 0 for patients not known to have preexisting organ dysfunction (JAMA. 2016; 315[8]:762-74). In addition, the concept of the quick SOFA (qSOFA) score was introduced as a possible predictive tool among encounters with suspected infection outside the intensive care unit.



INVISIONER/THINKSTOCK

These data were drawn from North American cohorts and a single German cohort and have not been validated externally."

For the current study, the main outcome of interest was to evaluate the effect of an increase in SOFA score of 2 or more points, 2 or more systemic inflammatory response syndrome (SIRS) criteria, and a qSOFA score of 2 or more points measured within the first 24 hours of admission in discriminating in-hospital mortality among patients with suspected infection admitted to ICUs (JAMA. 2017 Jan 17;317[3]:290-300).

A composite second outcome of interest was in-hospital mortality or an ICU length of stay of 3 days or more. To do so, the researchers retrospectively evaluated a cohort of 184,875 patients with an infection-related primary diagnosis who were admitted to 182 ICUs in Australia and New Zealand between 2000 and 2015. They applied SOFA, qSOFA, and SIRS criteria to data collected within 24 hours of ICU admission.

The mean age of the patients was 63 years, 45%

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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

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
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Distributed by

GlaxoSmithKline
Research Triangle Park, NC 27709

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Continued from page 27

were women, and the most common diagnosis was bacterial pneumonia (18%). Nearly 19% of patients died in the hospital and 56% died or experienced an ICU length of stay of at least 3 days or more.

The researchers found that the SOFA score increased by 2 or more points in 90% of patients, while 87% manifested 2 or more SIRS criteria, and 54% had a qSOFA score of 2 or more points. In addition, discrimination of in-hospital mortality was significantly higher using SOFA (area under the receiving operating characteristic curve [AUROC], 0.753), compared with both SIRS criteria (AUROC, 0.589) and qSOFA (0.607); the between-group difference reached a *P* value of less than .001.

Similar results were seen for the composite outcome of in-hospital mortality or an ICU length of stay of 3 days or more, which was higher using SOFA (AUROC, 0.736), compared with both SIRS criteria (AUROC, 0.609) and qSOFA (0.606); the between-group difference also reached a *P* value of less than .001.

The researchers acknowledged certain limitations of the study, including the fact that SOFA, SIRS criteria, and qSOFA could be studied only for the first 24 hours in the ICU.

"Biochemical and physiological values could have come from any time within the first 24 hours of ICU admission and, as a result, could not be more accurately linked to the timing of the diagnosis of infection," they wrote. "The SOFA score used should be considered a modification of the original because the cardiovascular component was estimated without knowledge of inotrope or vasopressor dose. The incidence of nosocomial infections and of infections in patients admitted with another diagnosis were unknown."

Three of the seven study authors disclosed that they receive salary support from Monash University in Melbourne. The remainder reported having no financial disclosures.

dbrunk@frontlinemedcom.com

VIEW ON THE NEWS

qSOFA still has a role in identifying high-risk patients

It is neither surprising that qSOFA did not perform as well as the SOFA score in the ICU, given that this finding was already reported by Seymour et al. in their initial work, nor is it critically important because qSOFA is more likely to be useful outside of the ICU setting.

Thus, the findings ... support the results reported by Seymour et al. that qSOFA is potentially helpful in settings outside the ICU in rapidly identifying patients with suspected infection who have, or will likely develop, sepsis (JAMA. 2016;315[8]:762-74).

qSOFA score still warrants further testing, however, particularly in lower- and middle-income settings where context (for example, timing of presentation to the hospital among patients with a suspected infection) might vary considerably and such contextual factors might affect predictive validity.

In addition, prospective studies may evaluate the utility of qSOFA when used longitudinally, with repeated measurements throughout the hospital stay.

Arguably, the highest-quality evidence for validation of any tool to support clinical decision making would come from an analysis to establish whether decisions made with the support of the tool lead to better patient outcomes than those made by clinical judgment alone.

Ultimately, the utility of qSOFA will likely become surpassed if and when highly accurate, rapid diagnostic tests for sepsis emerge.

For now, however, outside the ICU in the high-income settings where it has been tested, qSOFA appears a simple, rapid, inexpensive, and valid way to identify – among patients with suspected infection – those at a higher risk of having or developing sepsis.

Francois Lamontagne, MD, David A. Harrison, PhD, and Kathryn M. Rowan, PhD, are affiliated with the Intensive Care National Audit & Research Centre, London. Dr. Lamontagne reported serving as investigator for a study funded by GlaxoSmithKline and E-Motion. These comments are extracted from an editorial that appears in the Jan. 17, 2017, edition of JAMA (317[3]:267-8).

Early procalcitonin testing cut ICU costs in sepsis

BY JOSEPH CANTLUPE
Frontline Medical News

FROM CHEST

Procalcitonin (PCT) testing on the first day of ICU admission for adult patients with sepsis is associated with reduced length of stay, less antibiotic exposure, and reduced hospital and pharmacy costs, Robert A. Balk, MD, FCCP, and his associates reported.

The researchers analyzed data on more than 15 million patients in the Premier Research Database; of those, more than 730,000 patients had a potential diagnosis of sepsis, systemic inflammatory response syndrome (SIRS), septicemia, or a shock-related diagnosis upon ICU admission or discharge (CHEST. 2017;151[1]:23-33).

After propensity matching to reduce potential bias, a total of 33,569 patients who had received PCT testing on ICU day 1 were identified; a control group of 98,543 non-PCT tested patients were identified as well.

Hospital costs were $2,759 lower for PCT-tested patients ($30,454 vs. $33,213), ICU costs were $1,310 lower ($20,155 vs. $21,465), and pharmacy costs were $331 lower ($4,238 vs. $4,568). PCT-tested patients also were more commonly discharged to home (44.1% vs. 41.3%).

The PCT-tested patients had less total antibiotic exposure, (16.2 days vs. 16.9 days) but higher laboratory costs, according to Dr. Balk, director of the division of pulmonary and critical care medicine at Rush Medical College, Chicago, and his colleagues. Laboratory costs of the PCT-tested patients were $81 greater ($1,807 vs. $1,726).

While PCT testing is cleared by the Food and Drug Administration to assist in identifying patients who are highly likely to develop sepsis, there is no approved sepsis test, Dr. Balk and his colleagues noted.

"This study is important in the validation of the ability of PCT testing to favorably impact the outcome of critically ill patients when used according to the FDA cleared guidelines," the investigators said. "The cost savings were real and consequential, exceeding the potential increased costs of laboratory testing associated with PCT testing on ICU admission."

All-patient analysis showed a statistically significant, but slightly increased (0.7%) risk of mortality in PCT-tested patients; however, the finding was not seen in an enhanced risk-adjusted analysis of 96% of patients, the investigators pointed out. This finding is consistent with other large prospective studies showing no difference in mortality or other clinical outcomes using PCT guidances.

PCT testing has not been uniformly adopted despite its inclusion in the 2012 Surviving Sepsis Guidelines, in part, because of cost. The lack of a "gold standard" sepsis test has resulted in diagnostic dilemmas, delayed treatment, and poor outcomes, Dr. Balk and colleagues noted.

Because patients were not randomized to PCT testing or non-PCT testing groups, additional variables could have over- or underestimated the effect of PCT on patient outcomes, the researchers added.

Dr. Balk has received advisory board fees from bioMerieux USA and various other companies. Zhun Cao, PhD, Craig Lipkin, MS, and Scott B. Robinson MA, MPH, are employees of Premier Research Services, in Charlotte. Samuel Bozzette is an employee of bioMerieux, which provided funding for the study.

VIEW ON THE NEWS

Real-world evidence supports use of procalcitonin

The significant findings of Balk et al. suggest that "real-world" evidence may support procalcitonin as an effective tool to improve antibiotic management and reduce costs of health care for critically ill patients. Data from public databases and patient registries can play key roles in evaluating biomarkers, since physicians preparing randomized trials may behave differently than in typical care settings.

Results of the recent randomized [Simplified Acute Physiology Score] trial in connection with real-life data reported by Dr. Balk and colleagues are convincing and should lead physicians to more widespread use of PCT protocols for management of patients in the critical care settings.

The study findings also add the U.S. experience to the knowledge base as most of the interventional research has been done in Europe and Asia.

Given the promising results from the randomized trials, it is important to know how PCT impacts the clinical management of patients in real-world settings. Such information can be used to further broaden and expand the findings from the randomized trials to usual care.

Philipp Schuetz, MD, MPH, of the University of Basel, Switzerland, receives research support from Thermo Fisher and bioMerieux, which make PCT tests. Peter M. Wahl, ScD, is a full-time employee of Covance, of Princeton, N.J., which makes diagnostic tests and owns clinical laboratories. Their comments were made in an editorial accompanying Dr. Balk's report (Chest. 2017;151[1]:6-8. doi:10.1016/j.chest.2016.07.014).

Hypothermia does not benefit children post cardiac arrest

BY JENNIE SMITH
Frontline Medical News

Comatose children who survived cardiac arrest in the hospital do not benefit more from treatment with therapeutic hypothermia than from keeping their body temperatures normal, according to results from a randomized trial conducted in 37 hospitals in three countries.

The findings were presented in Honolulu at the Critical Care Congress, sponsored by the Society for Critical Care Medicine, and published online Jan. 24 in the New England Journal of Medicine (2017 Jan 24. doi: 10.1056/NEJMoa1610493). They add to a growing consensus from adult studies that the use of induced hypothermia to prevent fevers and neurologic injury after cardiac arrest does not confer additional survival or functional benefit over normothermia. Less was known about children, particularly those whose cardiac arrest occurred in a hospital setting.

Frank W. Moler, MD, of the University of Michigan, Ann Arbor, led the study, which randomized 329 comatose children, from newborns to age 18 years, to either 120 hours of normothermia (target temperature, 36.8° C) or 48 hours of hypothermia (33°) followed by normal temperature maintenance to 120 days following an in-hospital cardiac arrest.

Fever prevention in both groups was achieved through active intervention, with hypothermia-treated patients also having been pharmacologically paralyzed and sedated. The investigators used the Vineland Adaptive Behavioral Scales to measure neurobehavioral function, with a score of 70 or higher deemed indicative of good function.

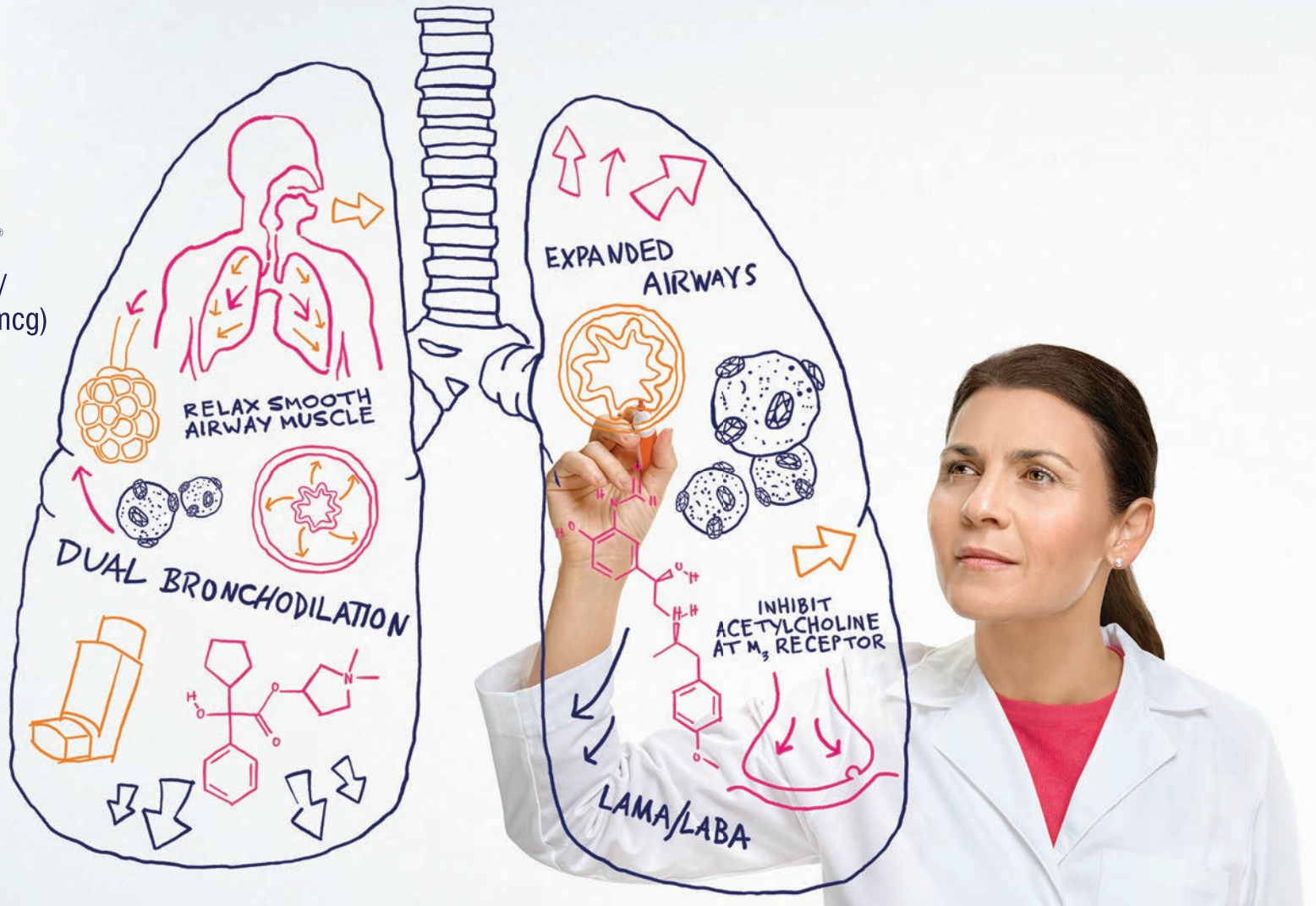
The study's primary outcome was survival at 12 months after cardiac arrest and a favorable neurobehavioral outcome.

In the 257 children with scores of 70 or higher before cardiac arrest, no significant differences were seen between the two different groups, with 36% of the hypothermia-treated patients (48/133) and 39% of normothermia-treated patients (48/124) surviving with a favorable neurobehavioral outcome (relative risk, 0.92; 95% confidence interval, 0.67-1.27; $P = .63$). In 317 children who could be evaluated for changes in neurobehavioral function, the changes from baseline between groups did not reach statistical significance ($P = .70$), and 1-year survival also did not differ significantly (49% for hypothermia-treated vs. 46% for normothermia; RR, 1.07; 95% CI, 0.85-1.34; $P = .56$). Adverse events did not differ significantly between groups.

The trial was stopped early for futility, leaving fewer than the hoped-for number of patients available for analysis, and wider confidence intervals. However, the investigators said their hypothesized a 15–percentage point benefit for hypothermia treatment could be ruled out. Dr. Moler and his colleagues wrote in their analysis that unanswered questions remain regarding the role of body temperature interventions in this population, noting that different duration of treatment, different temperatures, and combination of temperature management with neuroprotective agents are worth considering for future studies. Dr. Moler and his colleagues' study was funded by the National Heart, Lung, and Blood Institute. Four of its 49 coauthors disclosed commercial conflicts of interest.

BEVESPI
AEROSPHERE®

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



BEVESPI AEROSPHERE is indicated for the maintenance treatment of COPD.
It is not indicated for the relief of acute bronchospasm or for the treatment of asthma.

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

IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING

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

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

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

WARNINGS AND PRECAUTIONS

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

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

FOR THE MAINTENANCE TREATMENT OF COPD

DUAL BRONCHODILATION, DOWN TO A SCIENCE

INTELLIGENT FORMULATION*

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

MAXIMIZE BRONCHODILATION†

Improved lung function‡ vs placebo including[1]

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

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

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

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

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

LEARN MORE AT BEVESPIAEROSPHERE.COM

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

DRUG INTERACTIONS

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

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

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

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

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

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

AstraZeneca

BEVESPI AEROSPHERE™

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

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

WARNING: ASTHMA-RELATED DEATH

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

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

INDICATIONS AND USAGE

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

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

DOSAGE AND ADMINISTRATION

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

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

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

CONTRAINDICATIONS

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

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

WARNINGS AND PRECAUTIONS

Asthma-Related Death

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

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

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

Deterioration of Disease and Acute Episodes

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

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

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

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

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

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

Paradoxical Bronchospasm

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

Immediate Hypersensitivity Reactions

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

Cardiovascular Effects

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

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

Coexisting Conditions

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

Hypokalemia and Hyperglycemia

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

Worsening of Narrow-Angle Glaucoma

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

Worsening of Urinary Retention

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

ADVERSE REACTIONS

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

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

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

Clinical Trials Experience

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

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

24-Week Trials

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

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

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

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

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

Long-Term Safety Extension Trial

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

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

DRUG INTERACTIONS

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

Adrenergic Drugs

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

Xanthine Derivatives, Steroids, or Diuretics

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

Non-Potassium Sparing Diuretics

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

Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs

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

Beta-Blockers

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

Anticholinergics

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects:

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

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

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

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

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

Labor and Delivery

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

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

Hepatic Impairment

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

Renal Impairment

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

OVERDOSAGE

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

Glycopyrrolate

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

Formoterol Fumarate

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

Manufactured for: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

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

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Advantages of sleeve lobectomy in NSCLC confirmed

BY RICHARD MARK KIRKNER
Frontline Medical News

Guidelines that recommend sleeve lobectomy as a means of avoiding pneumonectomy for lung cancer have been based on a limited retrospective series, but a large series drawn from a nationwide database in France has confirmed the preference for sleeve lobectomy because it leads to higher rates of survival, despite an increased risk of postoperative pulmonary complications.

"Whenever it is technically possible, surgeons must perform sleeve lobectomy to provide more long-term survival benefits to patients, even with the risk of more postoperative pulmonary complications," said Pierre-Benoit Pagès, MD, PhD, and his coauthors in the January 2017 issue of the Journal of Thoracic and Cardiovascular Surgery (2017;153:184-95). Dr. Pagès is with the department of thoracic and cardiovascular surgery at the University Hospital Center Dijon (France) and Bocage Hospital.

The study involved 941 patients who had sleeve lobectomy and 5,318 who had pneumonectomy from 2005 to 2014 for localized non–small cell lung cancer in the Epithor Project database of the French Society of Thoracic and Cardiovascular Surgery, for whom Dr. Pagès and his coauthors performed the study. (Epithor is short for epidémiologie en chirugie thoracique, or epidemiology in thoracic surgery.)

Three-year overall survival was 71.9% for the sleeve lobectomy group vs. 60.8% for the pneumonectomy group. Three-year disease-free survival was 46.4% for the sleeve lobectomy group and 31.6% for the pneumonectomy group. In addition, compared with the sleeve lobectomy group, the pneumonectomy group had an increased risk of recurrence by matching (hazard ratio, 1.49; 95% confidence interval, 1.1-2).

The researchers performed a propensity-matched analysis that favored sleeve lobectomy for early overall and disease-free survival, but the weighted analysis did not. Patients in the sleeve lobectomy group vs. the pneumonectomy group were younger (60.9 years vs. 61.9), had higher body mass index (25.6 kg/m^2 vs. 25.1 kg/m^2), had higher average forced expiratory volume (74.1% vs. 62.9%), and had lower American Society of Anesthesiologists scores (73.7% with scores of 1 and 2 vs. 70.8%). Sleeve lobectomy patients also were more likely to have right-sided surgery (69.6% vs. 41%) and squamous cell carcinoma (54.6% vs. 48.3%), and lower T and N stages (T1 and T2, 60.5% vs. 40.6%; N0, 40.9% vs. 26.2%).

Overall mortality after surgery was 5% in the sleeve lobectomy group vs. 5.9% in the pneumonectomy group, but propensity scoring showed far fewer postoperative pulmonary complications in the pneumonectomy group, with an odds ratio of 0.4, Dr. Pagès and his coauthors said. However, with other significant complications – arrhythmia, bronchopleural fistula, empyema, and hemorrhage – pneumonectomy had a propensity-matched odds ratio ranging from 1.6 to 7. "We found no significant difference regarding postoperative mortality in the sleeve lobectomy and pneumonectomy groups, whatever the statistical method used," Dr. Pagès and his coauthors wrote.

The investigators had no financial relationships to disclose.

VIEW ON THE NEWS

Perform pneumonectomy 'sparingly'

The study by Dr. Pagès and his colleagues is unique in the field of surgery for non–small cell lung cancer in that it drew on a nationwide database using data from 103 centers, Betty C. Tong, MD, MHS, of Duke University Medical Center, Durham, said in her invited commentary (J Thorac Cardiovasc Surg. 2017;153:196). "These results are likely as close to real life as possible," she said.

She acknowledged that no prospective, randomized controlled trials have compared sleeve lobectomy to pneumonectomy, but she added, "it is unlikely that such a trial could be successfully executed." The 5:1 ratio of patients having pneumonectomy vs. sleeve lobectomy in this study is similar to findings from the Society of Thoracic Surgeons General Thoracic Surgery database (J Thorac Cardiovasc Surg. 2008;132:247-54), Dr. Tong pointed out, "and likely reflects the fact that sleeve lobectomy can be technically more difficult to perform."

The findings of the French Society of Thoracic and Cardiovascular Surgery group "should strongly encourage thoracic surgeons to perform pneumonectomy as sparingly as possible," and consider sleeve lobectomy the standard for patients with central tumors, Dr. Tong said.

She had no financial relationships to disclose.

Interatrial shunt benefits sustained for 1 year in HFpEF

BY MARY ANN MOON
Frontline Medical News

NEW ORLEANS – An interatrial septal shunt device continued to provide "sustained and meaningful clinical benefit" at 1-year follow-up for 64 patients who had heart failure with preserved ejection fraction (HFpEF), David M. Kaye, MD, PhD, reported at the American Heart Association scientific sessions.

The device is implanted via cardiac catheterization and is intended to reduce elevated left atrial pressure, particularly that associated with exertion, by allowing a small amount but not excessive left-to-right shunting. Patients showed improvements in 6-minute walk distance, New York Heart Association class, and HF-related quality of life scores at 6 months, and those effects persisted at the most recent (12-month) follow-up, he said in a presentation that was simultaneously published online in Circulation (2016 Nov 16).

REDUCE LAP-HF (Reduced Elevated Left Atrial Pressure in Patients With Heart Failure), a manufacturer-sponsored, nonrandomized, open-label study established the device's safety and performance in a relatively small group of patients. A larger, double-blind, randomized trial with sham controls is now underway "to validate the utility of this novel therapy," said Dr. Kaye of Alfred Hospital, Melbourne.

Overall survival at 1 year was 95%. Three patients died (one from combined pneumonia and renal failure, one from a fatal stroke, and one from an undetermined cause) and one was lost to follow-up. Thirteen patients required 17 hospitalizations for heart failure.

Six-minute walk distance improved from 331 meters at baseline to 363 meters. NYHA classification improved dramatically, as did quality of life scores as assessed by the Minnesota Living With HF questionnaire.

All 48 devices that were evaluable on echocardiographic imaging remained patent, showing continued left-to-right shunting. Left ventricular ejection fraction remained unchanged while right ventricular ejection fraction was significantly elevated over baseline levels. "In conjunction, there were modest but stable reductions in LV end-diastolic volume index with a concomitant rise in RV end-diastolic index," he said.

A subset of 18 study participants underwent heart catheterization during both rest and exercise so that hemodynamics could be assessed. Exercise time increased significantly, from 8.2 minutes at baseline to 9.7 minutes at 6 months and to 10.4 minutes at 1 year. Similarly, peak work capacity during supine cycling increased from 48 watts at baseline to 60 watts at 6 months and 55 watts at 1 year. These benefits occurred without any increase in pulmonary capillary wedge pressure.

Systemic blood pressure did not change over time, either at rest or during exercise. Left and right atrial volumes also remained unchanged.

Perhaps most importantly, Dr. Kaye said, right-sided cardiac output increased significantly, while left-sided cardiac output remained unchanged. There was no evidence of increased pulmonary pressure or pulmonary vascular resistance. This meant that patients could do more physical activity for a given level of left atrial pressure, he said.

To discussant Nancy K. Sweitzer, MD, PhD, the most important aspect of the 1-year results of REDUCE LAP-HF was the strong showing for device safety.

REDUCE LAP-HF was funded by Corvia Medical, maker of the shunt device. Dr. Kaye is an unpaid member of Corvia's scientific advisory group. Dr. Sweitzer is an investigator in the ongoing randomized trial of the interatrial shunt.

Tom Price said little on specifics for Medicaid reform

BY GREGORY TWACHTMAN
Frontline Medical News

WASHINGTON – Rep. Tom Price, MD (R-Ga.), dodged specifics on Medicaid reform and the issue of block grants for funding Medicaid during a hearing before the Senate Financing Committee.

The committee will be voting to move forward to the full Senate his nomination as secretary of the Department of Health & Human Services.


REP. PRICE

In his current role as congressman, Rep. Price has advocated for block grant funding for Medicaid. When pressed on whether he will continue to advocate for this approach, Rep. Price deferred to Congress for setting policy and said that he would enforce whatever direction taken by any upcoming reform law. He additionally called for better metrics to determine the quality of care, a measure that was not specifically tied to money spent on the program.

Sen. Robert Casey (D-Penn.) queried Rep. Price about guarantees as to whether people with disabilities covered by Medicaid would continue to be covered under a block grant program. Rep. Price responded that the "metrics that we will use [are] the quality of care and whether or not they are receiving that care."

Rep. Price added that he is committed "to make it so they have that [current level of existing] coverage or greater." Sen. Casey questioned whether that goal could be achieved, considering the amount of funding that could potentially be lost to a block grant program.

When further pressed on the 2017 budget he prepared as House Budget Committee chairman that included block grants for Medicaid, Rep. Price would not state clearly his promotion of the concept. Instead, he said he was committed to creating a system that is affordable, accessible, of high quality, and responsive to patient needs, as well as one that incentivizes innovation and provides choice.

Rep. Price was also pressed on his advocacy of high-risk pools, particularly for those who have high-cost, preexisting conditions and might not be able to get coverage in other areas of the reformed market. He voiced his support for such pools as well as for pools that would allow people without a common economic link, such as an employer, to band together for insurance coverage.

Sen. Debbie Stabenow (D-Mich.) noted that the history of high-risk pools has been less than stellar, with insurance rates typically 150%-200% higher than the rates of other plans and, typically, lifetime caps on coverage. Rep. Price additionally called for a "better" system that puts patients at the center of health care decisions. In response to discussion with Sen. Chuck Grassley (R-Iowa), Rep. Price said transparency, specifically in relation to the Physician Payments Sunshine Act,

Continued on following page

President Trump hits ground running on ACA repeal

BY GREGORY TWACHTMAN
Frontline Medical News

WASHINGTON – President Trump wasted no time in getting the executive branch's wheels in motion toward repeal of the Affordable Care Act.

Within hours of being sworn in as the 45th president of the United States on Jan. 20, he signed an executive order that announced the incoming administration's policy "to seek the prompt repeal of the Patient Protection and Affordable Care Act."

The order opens the door for federal agencies to tackle ACA provisions such as the individual mandate and its tax penalties for not carrying insurance, as well as other financial aspects of the ACA that impact patients, providers, insurers, and manufacturers.

President Trump directed the Health & Human Services department and other departments with ACA oversight to "exercise all authority and discretion available to them to waive, defer, grant exemptions from, or delay the implementation of any provision or requirement of the Act that would impose a fiscal burden on any State or a cost, fee, tax, penalty, or regulatory burden on individuals, families, health care providers, health insurers, patients, recipients of health care services, purchasers of health insurance, or makers of medical devices, products, or medications."

The order directs the secretaries of HHS, the Treasury department, and the Labor department to "exercise all authority and discretion available to them to provide greater flexibility to States and cooperate with them in implementing healthcare programs."

With this order, President Trump also set the stage for creating a framework to sell insurance products across state lines by directing secretaries with oversight of insurance markets to "encourage the development of a free and open market in interstate commerce for the offering of healthcare services and health insurance, with the goal of achieving and preserving maximum options for patients and consumers."

gtwachtman@frontlinemedcom.com

Senate takes first step toward repealing ACA

BY GREGORY TWACHTMAN
Frontline Medical News

With a procedural passed on party lines, the Senate has set the stage for the repeal of the revenue aspects of the Affordable Care Act.

Republican Senators will be using the budget reconciliation process, which will allow them to move forward with repealing certain provisions of the health care reform law without any Democratic support, although passage of any replacement will require some bipartisan support as Republicans do not have the required 60 votes to guarantee passage.

In a floor speech Jan. 11, Sen. Lamar Alexander (R-Tenn.), chairman of the U.S. Senate Committee on Health, Education, Labor, and Pensions, said Senate Republicans "plan to rescue those trapped in a failing system, to replace that system with a functional market, or markets, and then repeal Obamacare for good." Sen. Alexander noted the process will involve protecting the 11 million people who have purchased health insurance through the exchanges and that any future bill will keep the ban on coverage denials for preexisting conditions and the allowance of coverage of children up to the age of 26 who are on their parents' plans.

This reform effort will not address Medicare reform.

gtwachtman@frontlinemedcom.com

VIEW ON THE NEWS

Michael E. Nelson, MD, FCCP, comments: Independent of whether one has a favorable opinion of the Affordable Care Act (ACA), as a health care provider one must favor providing some medical care to all. The Congressional Budget Office has estimated that approximately 18 million people will lose their health care insurance if the ACA is repealed. Certainly, the uncertainty generated by the absence of an alternative plan, despite the promises, has kept everyone associated with the health care system uneasy about the future. Now imagine if one were a patient without health care insurance. I would like to remind all of our politicians of the words of our 35th president, John Kennedy, "Let us not seek the Republican answer or the Democratic answer, but the right answer. Let us not seek to fix the blame for the past. Let us accept our own responsibility for the future." I hope they are listening.

Continued from previous page

was "vital," and expanded the notion of transparency to include outcomes and pricing so that patients could have the best information to make decisions about their own health care.

It is "virtually impossible" for patients to know their true health care costs, Rep. Price said. To be informed, patients need better outcome measures, which would be "a priority" if he is confirmed as secretary.

Rep. Price also agreed that the Children's Health Insurance Plan should be extended, and when asked about extending the program for 5 years, he responded that "8 years would be better."

In the area of mental health, he suggested treatment models similar to those used to address physical health.

Rep. Price was not grilled on his investments at the Finance Committee hearing as he was at the Health, Education, Labor and Pensions Committee hearing, where he maintained he did nothing unethical or against the rules of the Senate.

Separate from the hearing, eight Democratic senators, led by Ranking Member Patty Murray of Washington, sent a Jan. 23 letter to the U.S. Securities and Exchange Commission to investigate whether Rep. Price potentially engaged in insider trading or other violations in relation to his specific purchase of stock in Innate Immunotherapeutics.

gtwachtman@frontlinemedcom.com

THE MORE

DIFFICULT THE CASE,

THE LESS DIFFICULT THE CHOICE OF HOSPITAL.

The Mount Sinai Hospital - National Jewish Health Respiratory Institute brings together a strong, integrated program for diagnosis and treatment of respiratory illness and lung disease. Our pulmonologists collaborate with specialists in related disciplines and work closely with research scientists on precision medicine, genomics, and data-driven clinical protocols to enhance the quality and outcomes of the respiratory disease practice. Additionally, our experts are on the faculty of the Icahn School of Medicine at Mount Sinai, ranked among the nation's top medical schools by *U.S. News & World Report*.

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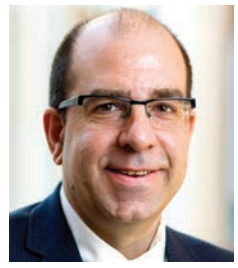
Meet the CHEST President-Designate


DR. COWL

Clayton T. Cowl, MD, FCCP, is the CHEST President-Designate and sits as a member of the Board of Regents. Dr. Cowl's presidential term will be 2018-2019. He currently is the Chair of the Division of Preventive, Occupational, and Aerospace Medicine with a joint appointment in the Division of Pulmonary and Critical Care Medicine at Mayo Clinic in Rochester, Minnesota.

Dr. Cowl is triple board-certified in Pulmonary and Critical Care Medicine, Occupational Medicine, and Internal Medicine, with an interest in airway disorders, occupational-related respiratory health, toxicology, altitude physiology, and transportation medicine.

His research focus has included projects in altitude physiology at Mayo Clinic's altitude chamber and testing for the emergency oxygen passenger mask in the Boeing 787 airliner. He has also published in the areas of occupational asthma and toxic inhalations.

At CHEST, Dr. Cowl has served as the Chair of the Pulmonary Board Review Course and as a member of the SEEK Editorial Board. He is on the Board of Directors of CHEST Enterprises and has served as a subject matter expert and faculty for Professional Representative Education Program (PREP) courses.

He is currently the President of the Civil Aviation Medical Association and is a Senior Aviation Medical Examiner designated by the Federal Aviation Administration.

Dr. Cowl has been a recipient of the Innovation in Education Award from the Mayo School of Continuous Professional Development, and the Laureate Award in the Mayo Clinic Department of Medicine.

CHEST Foundation can give more than $500,000 in grants

Every year, the CHEST Foundation awards more than a half-million dollars in grants to the next generation of lung health champions. February 2017 marks the start of the foundation's next grant cycle, and we are excited to announce a new clinical research grant in Cystic Fibrosis, among many other disease-state topics. In 2016, the foundation awarded 11 CHEST members for their innovative and inspiring research proposals and community service programs.

"I am very proud to have been awarded a CHEST Foundation grant and pleased that clinical research and real-world evidence are a priority to the foundation," stated Alice Turner, MBChB, PhD. Dr. Turner was awarded the 2016 CHEST Foundation and the Alpha-1 Foundation Clinical Research Grant in Alpha-1 Antitrypsin Deficiency. "This award means that my patients can now see publicly the efforts that are being made to reduce inequities in care and ensure that the best treatments are made available in the UK."

The award will allow Dr. Turner to compare patients who are being treated in the United States with those who are untreated in the United Kingdom and then analyze the effects on mortality, hospitalization, and quality of life to make inferences about whether or not the treatment should be implemented in the United Kingdom. Currently, the type of treatment used to treat patients with alpha-1 antitrypsin deficiency in the United States is not available in the United Kingdom, and the results of this study will be provided to the National Health Service in England to help overcome the barriers of legalizing the treatment in the United Kingdom.


Left to right: Clemens Grassberger, PhD - CHEST Foundation Research Grant in Lung Cancer; Don Hayes Jr., MD, FCCP - GlaxoSmithKline Distinguished Scholar in Respiratory Health; Peter Leary, MD, MS - CHEST Foundation Research Grant in Pulmonary Arterial Hypertension; Catherine Oberg, MD - CHEST Foundation Research Grant in Women's Lung Health; Farbod Rahaghi, MD, PhD - CHEST Foundation Research Grant in Venous Thromboembolism; Brett Ley, MD - CHEST Foundation Research Grant in Pulmonary Fibrosis; and Joseph Huang, MD - Accepting the award on behalf of E. Jane Carter, MD, FCCP, for CHEST Foundation Community Service Grant Honoring D. Robert McCaffree, MD, Master FCCP.

Sydney Montesi, MD, was awarded the CHEST Foundation Research Grant in Pulmonary Fibrosis for her work on using noninvasive lung imaging to see how contrast agents can be used to measure disease activity and progression.

"As a provider, it can be very difficult when we first meet a patient to know what disease course they will take, but if we had this information, it would help us in determining earlier lung transplant referrals, choosing the best therapies and treatments, and ultimately lowering the mortality rate of idiopathic pulmonary fibrosis," Dr. Montesi said of her research. "Receiving this grant is essential because it will allow us to test our hypothesis that vascular leakage is increased in patients with pulmonary fibrosis, and we will also be able to look more in depth at the comparison of patients with stable disease and those with progressive disease."

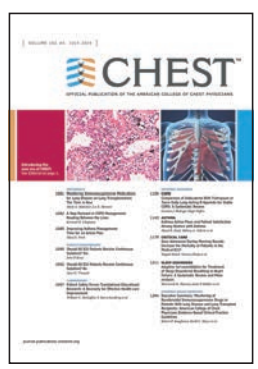
These grants help advance the work of young investigators all over the globe. Over the last 20 years, thousands of researchers and community service volunteers have received more than $10 million in funding.

Beginning in February 2017, the Foundation will have more than a half-million dollars available in funding toward the next generation of lung health champions.

Learn more about the CHEST Foundation grant application process at chestnet.org/grants or e-mail the foundation at grants@chestnet.org.

This Month in *CHEST*: Editor's Picks

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



EDITORIAL
GOLD 2017: A New Report By Dr. P. J. Barnes

ORIGINAL RESEARCH
Estimating Ten-Year Trends in Septic Shock Incidence and Mortality in United States Academic Medical Centers Using Clinical Data. By Dr. S. S. Kadri, et al.

Long-term Outcomes of Patients With Ground-Glass Opacities Detected Using CT Scanning. By Dr. S. Sawada, et al.

ICU Telemedicine Program Financial Outcomes. By Dr. C. M. Lilly et al.

Accuracy of Lung Ultrasonography in the Diagnosis of Pneumonia in Adults: Systematic Review and Meta-Analysis. By Dr. A. M. Llamas-Álvarez, et al.

EVIDENCE-BASED MEDICINE
Cough in the Athlete: CHEST Guideline and Expert Panel Report. By Dr. L-P Boulet, et al, on behalf of the CHEST Expert Cough Panel.

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

For appropriate adult patients

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

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

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

BREO is NOT indicated for the relief of acute bronchospasm.

Important Safety Information

WARNING: ASTHMA-RELATED DEATH

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

BOXED WARNING CONTINUED ON NEXT PAGE

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

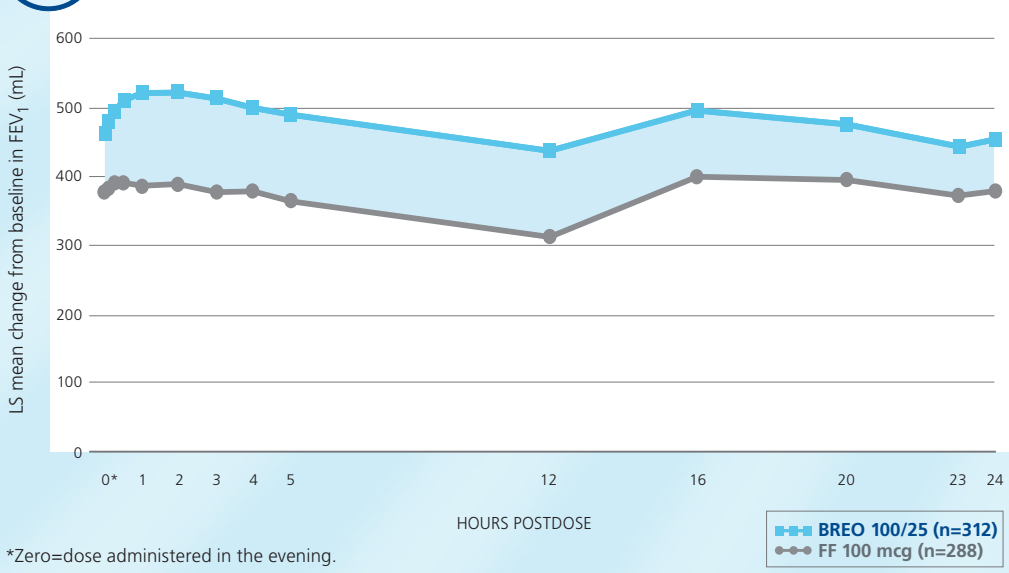
BREO:
CONTINUOUS LUNG FUNCTION IMPROVEMENT

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

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

BREO 100/25

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



*Zero=dose administered in the evening.

Study description

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

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

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

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

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

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

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

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

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

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

Important Safety Information (cont'd)

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

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

CONTRAINDICATIONS

The use of BREO is contraindicated in the following conditions:

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

WARNINGS AND PRECAUTIONS

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

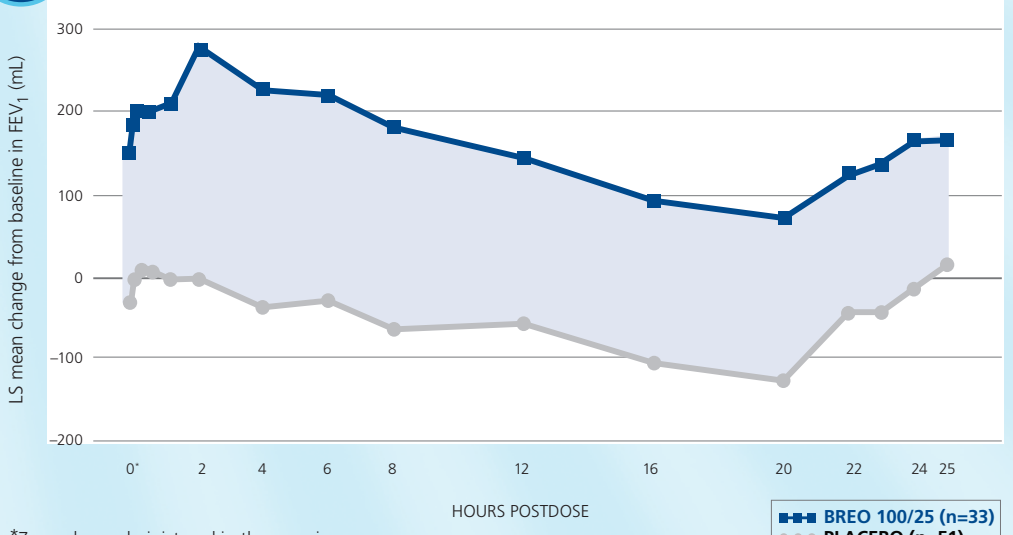
FOR A FULL 24 HOURS, WITH JUST ONE DAILY INHALATION

In patients with **COPD**

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

BREO 100/25

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



*Zero=dose administered in the morning.

Study description

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

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

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

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

FVC=forced vital capacity.

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

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

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

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

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

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

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

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

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

CONSIDER **24-HOUR BREO** TODAY

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

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

ADVERSE REACTIONS: BREO 100/25 FOR COPD

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

ADVERSE REACTIONS: BREO FOR ASTHMA

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

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

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

BREO ELLIPTA was developed in collaboration with Theravance

www.BREOprof.com

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

BRIEF SUMMARY

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

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

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

WARNING: ASTHMA-RELATED DEATH

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

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

1 INDICATIONS AND USAGE

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

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

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

5 WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6 ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

7 DRUG INTERACTIONS

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

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

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

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

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

8 USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

GlaxoSmithKline
Research Triangle Park, NC 27709

Revised 7/2016 BRE:7BRS

CRITICAL CARE COMMENTARY: Highlights from the 2016 hospital-acquired and ventilator-associated pneumonia guideline

BY ANDRE C. KALIL, MD, MPH; AND MARK L. METERSKY, MD, FCCP

The 2016 hospital-acquired and ventilator-associated pneumonia guidelines, sponsored by the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS), and endorsed by the American College of Chest Physicians (CHEST), Society of Critical Care Medicine (SCCM), and the Society for Healthcare Epidemiology, was published recently (Kalil AC, Metersky ML, Klompas M, et al. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis.* 2016 Sep 1;63[5]:575-82).


DR. KALIL


DR. METERSKY

This Critical Care Commentary aims to provide the highlights of the new guideline and to motivate readers to read the complete report that best represents the primary intent of the guideline panelists.

First, we would like to clarify the main goal, and what was not covered by this guideline. The main goal was to address the most relevant clinical questions regarding the diagnosis and treatment of hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP). Prevention of HAP/VAP was not assessed because recent guidelines were published by the Society for Healthcare Epidemiology of America; same for the ventilator-associated events (VAE), which are used for VAP surveillance. The immunocompromised population was not evaluated separately since they require alternative approaches related to their unique causes of immunosuppression. After an extensive literature review and face-to-face meeting discussion, the guideline panel decided to remove health-care–associated pneumonia (HCAP) from the new guidelines. The body of evidence suggests that most patients with HCAP are not at increased risk for multidrug-resistant (MDR) infections; they are more similar to patients with community-acquired pneumonia (CAP) than are patients with HAP or VAP. Its diagnostic and therapeutic approach aligns better with CAP; thus, the panel suggested that HCAP should be addressed by the upcoming CAP guideline.

The new guideline was written using the Grading of Recommendations Assessment, Development, and Evaluation methodology. This was the framework to address all clinical questions referred to as PICOs (patient; intervention; comparator; outcome), which can be explicitly seen in the published guideline. For every PICO question, the wording "we suggest" was used for a weak recommendation (lack of high confidence; further evidence could change it), and "we recommend" was used for a strong recommendation (high confidence; further evidence is unlikely to change it). Also, part of the panel framework was the requirement to disclose any actual, potential, or perceived conflicts of interest for each panelist to be accepted to participate, as well as to remain in the panel for the duration of the process. The cochairs remained free of any financial conflicts during the entire process.

The diagnosis of suspected HAP and VAP should include cultures of respiratory and blood samples. Based on the evidence that invasive respiratory sampling does not improve patient outcomes, may potentially delay the diagnostic process, and increase risks, the panel gave preference to noninvasive sampling with semiquantitative cultures. Recognizing that there may be specific clinical situations in which invasive sampling with quantitative cultures may be helpful, if a bronchoscopy is performed, the panel suggested that antibiotics may be withheld rather than continued if the quantitative results are below the diagnostic threshold for pneumonia. The use of biomarkers and clinical scores for the diagnosis for HAP and VAP were extensively evaluated by the panel, and the final recommendation was that clinical criteria alone, rather than using biomarkers (ie, C-reactive protein, procalcitonin, and soluble triggering receptor expressed on myeloid cells) or clinical pulmonary infection score, should be used to decide whether or not to initiate antibiotic therapy. Another diagnostic category evaluated was the controversial ventilator-associated tracheobronchitis (VAT). The evidence for this category is based on low-quality evidence, mostly from observational studies, beset by inconsistent findings, derived from single centers and not associated with survival outcomes. These significant limitations, in conjunction with the concern for excessive use of unnecessary antibiotics, prompted the panel to recommend against routine antibiotic therapy for these patients.

Choosing an empiric antibiotic regimen for patients with HAP and VAP requires balancing the potentially competing goals of ensuring that likely infecting pathogens are covered while avoiding excess antibiotic use.

Choosing an empiric antibiotic regimen for patients with HAP and VAP requires balancing the potentially competing goals of ensuring that likely infecting pathogens are covered while avoiding excess antibiotic use. In order to guide clinicians on empiric antibiotic therapy, the panel performed a comprehensive review of the potential risk factors for HAP and VAP. For VAP, three factors associated with disease severity (septic shock at time of VAP, ARDS preceding VAP, and acute renal replacement prior to VAP onset) and two epidemiologic factors (prior use of IV antibiotic use within 90 days, and 5 or more days of hospitalization prior to the occurrence of VAP) made the final risk factors list. For HAP, only the prior use of IV antibiotics within 90 days was associated with risk for MDR. However, because of the limitations and small number of studies on HAP only, the panel decided to add risk factors for mortality (ventilator support for HAP and septic shock) as surrogates for MDR risk factors in patients with HAP, as these factors presumably increase the risk of poor outcomes if there is initial inadequate empiric therapy.

In conjunction with the bedside evaluation of risk factors for MDR, the guideline recommends the use of local antibiograms not only to guide empiric therapy but also to decide if antibiotic coverage for MDR is needed. Ideally, the antibiogram should be based on the specific ICU, but if this is not feasible, or the hospital is of small size, an institutional antibiogram can also be helpful. The first benefit of local antibiograms is derived from the knowledge gained regarding the prevalence of each microorganism; for example, if only 3% of all VAP or HAP in a given unit or hospital is caused by *Pseudomonas aeruginosa*, it is likely that an empiric coverage for this microorganism will neither be necessary nor appropriate for most patients. The second benefit is derived from the knowledge concerning the frequency of MDR microorganisms within the unit or hospital: for example, patients with VAP in units where 10%-20% of *Staphylococcus aureus* isolates are resistant to methicillin, or greater than 10% of gram-negative isolates are resistant to an agent being considered for monotherapy, should receive antibiotics for MDR infections. With these two critical pieces of information, the clinician will have a higher probability of starting the correct empiric antibiotics, and, consequently, improve the survival outcomes of patients with HAP and VAP.

The choice of the empirical treatment of VAP and HAP becomes a natural derivation of the three main factors discussed above: (1) epidemiologic history of antibiotics' use and prior hospitalization length, (2) local antibiogram for the prevalence and resistance of microorganisms, and (3) disease severity and risk of mortality by the identification of septic shock, ARDS, and acute renal replacement therapy. For example, if 17% of all VAPs in your unit is from *P aeruginosa* (which is the national prevalence in patients with VAP), and 8% of these strains are resistant to an agent being considered for gram-negative monotherapy, not prescribing double coverage for *P aeruginosa* would still result in initial appropriate therapy in 98.6% (derived from 1-[0.17 x 0.08]) of cases. The reason why the panelists chose the threshold of 10% for *P aeruginosa*, and 10%-20% for *S aureus*, was based on the national prevalence rates reported by the Centers for Disease Control and Prevention, with the goal of limiting the initial inappropriate antibiotic therapy decision to less than 5% of all cases. We strongly believe that this "epidemiologic/antibiogram/disease severity" approach to select the empiric therapy is both clinically intuitive and essential to improve patients' outcomes. Further,

Continued on following page

CCSC issues five Choosing Wisely recommendations

Overutilization of tests, treatments, and procedures is an important example of low-value care that adds to the high cost of health care and provides little to no benefit for patients. To combat this problem, the American Board of Internal Medicine Foundation developed the Choosing Wisely Campaign, tasking professional societies to develop lists of the top five medical services that patients should question.

The Critical Care Societies Collaborative (CCSC), which comprises the four major U.S. professional and scientific societies – the American Association of Critical-Care Nurses, the American College of Chest Physicians, the American Thoracic Society, and the Society of Critical Care Medicine – participated by creating a task force that addressed this task to focus on critical care delivery.

Five CCSC recommendations were formulated:

1. Don't order diagnostic tests at regular intervals (such as every day), but rather in response to specific clinical questions.

2. Don't transfuse red blood cells in hemodynamically stable, nonbleeding patients with a hemoglobin concentration greater than 7 mg/dL.

3. Don't use parenteral nutrition in adequately nourished critically ill patients within the first 7 days of an ICU stay.

4. Don't deeply sedate mechanically ventilated patients without a specific indication and without daily attempts to lighten sedation.

5. Don't continue life support for patients at high risk for death or severely impaired functional recovery without offering patients and their families the alternative of care focused entirely on comfort.

The CCSC is tracking use/implementation of the Choosing Wisely recommendations among its four member organizations. Please complete this short survey at https://redcap.rush.edu/redcap/surveys/?s. Please click submit when finished.

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this approach will substantially reduce the unnecessary use of double antibiotic therapy in patients with VAP or HAP.

This guideline suggests that the use of inhaled antibiotic therapy in conjunction with IV antibiotics may benefit patients with VAP or HAP from MDR microorganisms that are sensitive to only polymyxins or aminoglycosides. The panel also suggested that the use of pharmacokinetic and pharmacodynamics should be used to optimize the administration of antibiotic therapy for all patients with HAP or VAP.

Last, after an extensive review and multiple analyses of all available evidence, the panel concluded that the majority of patients with HAP or VAP should be treated with 7 days of therapy, independent of the microorganism causing the pneumonia. In several meta-analyses performed by the panelists to evaluate all patients with VAP, as well as only patients with VAP caused by nonfermenting gram-negative organisms such as *Pseudomonas* species, *Stenotrophomonas* species, and *Acinetobacter* species, the panel did not find differences between short and long courses of antibiotics regarding mortality, clinical cure, pneumonia recurrence, and mechanical ventilation duration. In recognition of the individual needs of each patient, we made a remark that shorter or longer duration of antibiotics may be indicated, depending upon the rate of improvement of clinical, radiologic, and laboratory parameters. Several adjunctive methods of deescalation were assessed, but only procalcitonin was suggested to aid health care providers to shorten the course of antibiotic therapy.

In conclusion, the authors of this 2016 HAP/VAP IDSA/ATS guideline hope to achieve the ultimate goal of improving the treatment and outcomes of patients with HAP and VAP and reducing unnecessary antibiotic use.

Dr. Kalil is with the department of internal medicine, division of infectious diseases, University of Nebraska Medical Center, Omaha; Dr. Metersky is with the division of pulmonary and critical care medicine, University of Connecticut, Farmington.

PCCM endorsed as pilot subspecialty by the Chinese National Health and Family Planning Commission

On Dec. 23, 2016, the Chinese National Health and Family Planning Commission officially endorsed Pulmonary and Critical Care Medicine (PCCM) as a pilot subspecialty within China. PCCM is one of three subspecialties (together with neurosurgery and cardiology) to pioneer fellowship training education in China. With the official endorsement of PCCM, local efforts will progress within China to administer programs and extend the standards of training throughout medical education in China. PCCM certification will now become a requirement for appointment of pulmonary department chairs and for promotion within the subspecialty.

Since 2012, CHEST has worked closely with partners, such as the Chinese Thoracic Society, the Chinese Association of Chest Physicians, and the Chinese Medical Doctor Association, on the development of China's first fellowship program offering standardized training in PCCM for Chinese physicians. As a result of these collective efforts, PCCM has now officially earned endorsement as a medical subspecialty – the first of its kind in a country where medical training typically ends after a physician completes residency training. Only a decade ago, physicians in China went directly into practice following medical school. The development of a PCCM subspecialty in China – made possible through the engagement of CHEST's expert faculty and administration – parallels what has occurred over the past 3 decades in the United States, during which the fields of pulmonary and critical care medicine evolved into the combined subspecialty of PCCM.

The China-CHEST PCCM Fellowship Program was officially launched in 2013 with 12 participating Chinese institutions starting their PCCM training programs. By the end of 2017, 30 programs with 300 fellows and 60 faculty will be participating at institutions throughout China, with the potential to impact the care of thousands of patients. The China-PCCM Fellowship Program proudly graduated its first class of fellows in September 2016.

China-CHEST leaders, including Renli Qiao, MD, PhD, FCCP; Chen Wang, MD, PhD, FCCP; and Jack Buckley, MD, MPH, FCCP; with Steve Welch, CHEST Executive Vice President, recently participated in local site visits to provide ongoing education and support to Chinese PCCM fellowship programs. They also participated in the November 2016 Mingdao Forum in Beijing to highlight the history and achievements of the China-CHEST PCCM program.

The vast reach and clinical exposure of this program highlights how an international professional medical association like CHEST, through innovative education and strategic collaborative partnerships, is able to impact medical training both within and beyond its specialty on a global scale.

Darcy Marciniuk, MD, FCCP
Chair, China–CHEST PCCM Steering Committee
Professor of Medicine, University of Saskatchewan,
Saskatoon, SK, Canada

Renli Qiao, MD, PhD, FCCP
Medical Director, China–CHEST PCCM Program
Professor of Clinical Medicine,
Keck School of Medicine of USC,
Los Angeles, California

Robb Rabito, CHCP
Director, Education Operations
CHEST
Glenview, Illinois

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Clinical Research

The unrecognized battlefield in our hospitals: Lessons from the US Navy SEALs

Burnout syndrome (BOS) is a psychological state resulting from prolonged exposure to job stressors. It is characterized by a vicious cycle of emotional exhaustion, detachment from others, and a feeling of decreased accomplishment. Severe BOS is seen in up to 45% of physicians and 33% of nurses who work in ICUs.[1]


DR. AMALAKUHAN

BOS has far-reaching consequences, being associated with an alarmingly high prevalence of posttraumatic stress disorder (PTSD) and substance abuse, almost equivalent to that experienced by veterans returning from war.[2] BOS also is associated with self-reported suboptimal patient care practices.[3]

This crisis has long been underrecognized, but now that we have identified the problem, where does that leave us? There are currently no quality studies evaluating how to best treat and prevent BOS/PTSD in health-care professionals. Previous studies have focused on addressing organizational factors to alleviate job stressors, but the psychosocial characteristics of the individual have been largely ignored.

Our medical education has historically focused on an individual's intelligence quotient (IQ), but developing an individual's emotional quotient (EQ) is just as valuable. It has long been known that Navy SEALs have the lowest prevalence of PTSD among combat veterans due partially to their specific training in emotional resilience and adaptive psychosocial coping mechanisms.

For this reason, the research team at the University of Texas Health Science Center at San Antonio is collaborating with the US Navy SEAL team to design and validate a tool that teaches critical care staff resilience training similar to what their combat trainees undergo. The goal is to curb these alarming trends in BOS and create a paradigm shift in medical education within medical and nursing schools.

Bravein Amalakuhan, MD
Fellow-in-Training Member

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Critical Care

End of the era for age of blood concerns?

Blood transfusions are common in critically ill patients, with two in five adults admitted to an ICU receiving a transfusion.[1,2] Recently, randomized trials have found that more restrictive thresholds for transfusions are associated with improved outcomes.[3,4] One theorized explanation for this somewhat counterintuitive association is that the prolonged storage time (i.e., the age of the blood being transfused) might affect outcomes.


DR. CARROLL


DR. GREENBERG

There have been three recent publications that help to shed some more light on this. First, Lacroix et al.[5] performed a multicenter randomized blinded trial in over 2,400 critically ill patients in 64 centers comparing new blood (mean storage (±SD) of 6.1±4.9 days) vs old blood with storage of 22.0±8.4 days (*P* less than .001). There was no statistically significant difference in 90-day mortality.[5]

The second study is a meta-analysis by Alexander et al.[6] The investigators looked at 12 trials and 5,229 patients and compared "fresh blood" or blood stored for 3-10 days to "older blood" stored for longer durations. They found that there was no difference in mortality and no difference in adverse events, such as acute transfusion reactions, when comparing the two groups.

Lastly, Heddle et al.[7] conducted a randomized trial that compared outcomes in 20,858 hospitalized patients transfused with fresh blood (mean storage time 13.0±7.6 days) to older blood (mean storage time 23.6±8.9 days). They found no differences in mortality when comparing those transfused with fresh vs. old blood (8.7% vs. 9.1%). In addition, there was no difference when examining the predetermined subgroups, including those undergoing cardiovascular surgery, those with cancer, and those admitted to the ICU.

So, is this the end of an era for health-care provider concern about how long blood can be stored to be safe for ICU patients? Possibly.

There may still be high-risk populations (such as patients receiving massive transfusions) for which age of the blood does matter. In addition, it is still unclear based on the present

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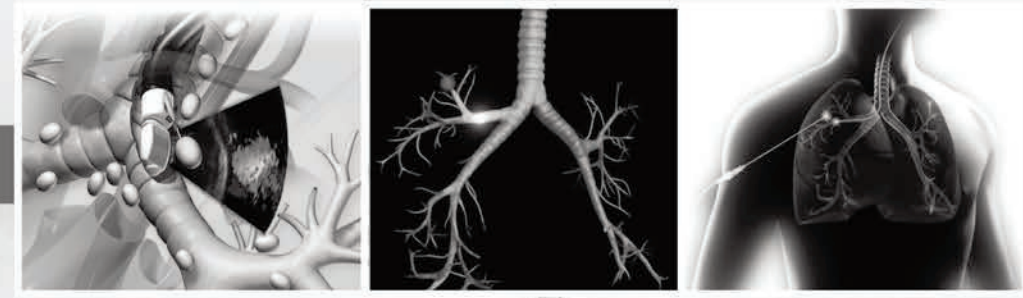

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data as to whether blood stored between 35 and 42 days has any significant inherent risk.

However, these publications among others suggest that the age of transfused blood may not matter, even in critically ill patients. Therefore, the present storage practices of many blood banks around the United States and beyond are validated by the present publications regarding the scarce resource of blood.

Christopher L. Carroll, MD, MS, FCCP
Steering Committee Member

Steven Greenberg, MD, FCCP
Steering Committee Member

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Airways Disorders

Inhaled corticosteroids in COPD: When to hold and when to fold

The 2017 GOLD guidelines reiterated that inhaled corticosteroids (ICS) be reserved for COPD patients with continued symptoms and exacerbations, despite use of long-acting beta-agonists (LABAs) and long-acting muscarinic agents (LAMAs). ICS are appropriate in approximately 40% of patients; however, prescribing rates can exceed 80% (Yawn et al. 2016; *Primary Care Respir J.* 26:16068).


DR. BLAIVAS


DR. RAMESH

Recent literature has begun to define the appropriate use of ICS in COPD. ICS/LABA combinations improve outcomes in patients with moderate to very severe COPD with frequent exacerbations. However, ICS/LABA may not further diminish exacerbation risk compared with those treated with a LABA/LAMA combination (Wedzicha et al., *N Engl J Med.* 2016;374:2222).

While the addition of LAMA to an ICS/LABA combination (triple therapy) improved lung function and decreased exacerbation risk, the addition of ICS to LABA/LAMA combination did not decrease exacerbations (GOLD Guidelines 2017). It has been suggested that those with asthma-COPD overlap identified by sputum eosinophilia represent ideal candidates for ICS therapy (GINA Guideline 2016).

ICS use in COPD increases pneumonia risk. The risk was highest in the very group for which guidelines recommend its use – those with a FEV_1 less than 50% of predicted or with prior COPD exacerbation (Ernst et al. *Eur Respir J.* 2015;45:525).

ICS may be safely withdrawn in low-risk patients (FEV_1 less than 50% predicted and no exacerbations in the previous year [Yawn et al.]).

In a trial comparing patients with severe COPD (FEV_1 less than 50%) on continued LAMA/LABA/ICS triple therapy vs LAMA/LABA with ICS withdrawal, the risk of moderate or severe exacerbations at 52 weeks was not increased (Magnussen et al. *N Engl J Med.* 2014;371:1285).

Conclusions

Based on the 2017 GOLD guidelines:

- Monotherapy with ICS is not recommended in COPD.
- In patients with continued respiratory-related symptoms without exacerbations (GOLD group B), LAMA or LABA or LAMA/LABA combination is recommended. There is no recommendation for ICS in this group.
- In patients with frequent exacerbations (GOLD groups C and D), LAMA/LABA combinations are preferred to LABA/ICS because of superior effectiveness (especially in Group D) and the increased pneumonia risk with ICS. Escalation to triple therapy can be considered if there are continued exacerbations.

Allen Blaivas, DO, FCCP
Steering Committee Member

Navitha Ramesh, MD, MBBS
Fellow-in-Training Member

Home-Based Mechanical Ventilation and Neuromuscular Disease

Advances in neuromuscular disease

Spinal muscular atrophy (SMA) type 1 is the most deadly inherited disease among infants, with most infants dying by 1 to 2 years of age without supportive therapies, such as assisted ventilation. It is caused by homozygous deletions or mutations in the survival motor neuron 1 (*SMN1*) gene. Disease severity varies in part depending on the number of backup *SMN2* gene copies that can produce some functional SMN protein (Arnold et al. *Muscle Nerve.* 2015;51[2]:157).


DR. MAZI

Recent developments of disease-modifying agents are giving hope to individuals with SMA and their families. Nusinersen (an antisense oligonucleotide) is an intrathecal medication that increases the production of functional SMN protein by increasing SMN2 exon 7 transcription (Chiriboga et al. *Neurology.* 2016;86[10]:890).

A recent open-label clinical trial by Finkel et al. (*Lancet.* 2017;388[10063]:3017) showed a "promising clinical response" that altered the natural history of disease progression. Most infants treated with multiple intrathecal doses of nusinersen had incremental improvement in their motor milestones and motor function ($P = .008$), as well as improved survival and/or avoidance of ventilation ($P = .0014$).

Moreover, the study found significant uptake of nusinersen by the motor neuron throughout the spinal cord and other neurons throughout the CNS. It appeared to be well tolerated. Disease-modifying medications may soon become "game changers" in many neuromuscular conditions.

However, a significant concern is the expected prohibitive cost both of a rare-disease-modifying therapy and of administrating intrathecal medications to fragile infants. As such, those obstacles will need to be overcome as neuromuscular clinics, hospitals, and payers start planning for the coming advances that our patients will be expecting.

Ahlam Mazi, MBBS
Fellow-in-Training Member

Interstitial and Diffuse Lung Disease

New advancements in predictive risk factors of IPF

In the last few years, many predictive risk factors were studied in clinical trials monitoring idiopathic pulmonary fibrosis (IPF), such as forced vital capacity and diffuse lung capacity for carbon monoxide (King TE Jr, et al. ASCEND Study Group. *N Engl J Med.* 2014;18;371-[12]:1172; Richeldi L, et al. INPULSIS Trial Investigators. *N Engl J Med.* 2015;20;373[8]:782; Ley B, et al. *Am J Respir Crit Care Med.* 2016;15;194[6]:711).


DR. CARBONE

Recent data that have not yet been published by Carbone et al evaluate the prognostic value of the New York Heart Association index (NYHA) compared with high resolution CT scan, somatostatin receptor scintigraphy (octreoscan), and echocardiography in a study population of 128 patients suffering from IPF (61% male subjects), nonspecific interstitial pneumonia, and granulomatous lung diseases (alveolitis, sarcoidosis, granulomatosis with polyangiitis). All patients were confirmed histologically.

The NYHA came out as a reliable prognostic factor in each setting. In fact, the log-rank test showed significant differences among NYHA categories, as cases included with disease showed the worst survival rate while no death cases were observed when NYHA was negative.

Moreover, the prognostic value of NYHA was confirmed by multivariate analysis, where the survival rate results were significantly different among patients with level 7 after adjustment for other variables included in the model.

Furthermore, the prognostic value of the NYHA index was once again confirmed when the analysis was limited to cases with the histological pattern of IPF (usual interstitial pneumonia).

The authors, therefore, strongly recommend utilization of the NYHA index as a prognostic factor of IPF as well as granulomatous lung diseases.

Roberto Carbone, MD, FCCP
Steering Committee Member

A. Monselise, MD, PhD
NetWork Nonmember

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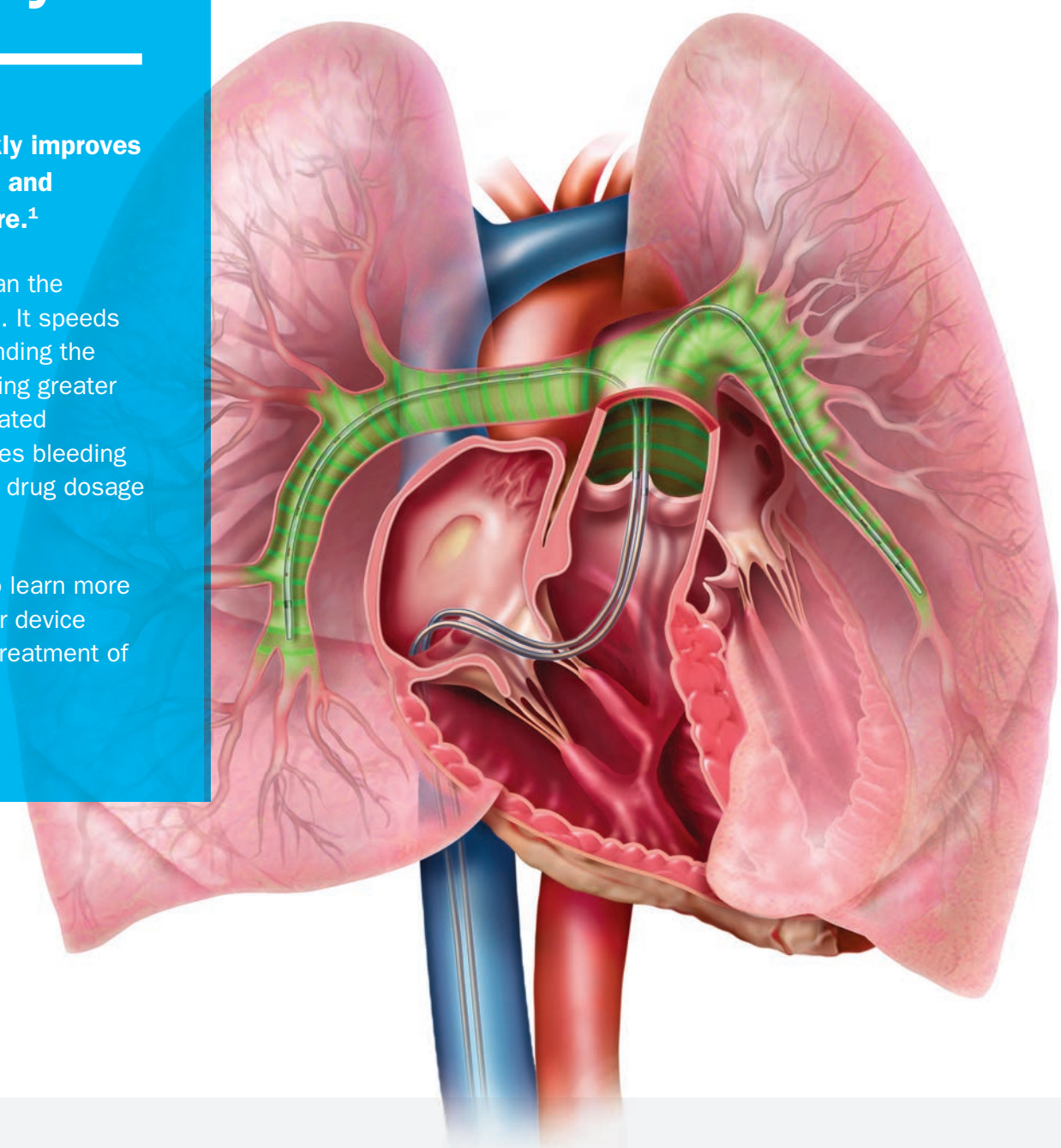

1 *In the Seattle II study of 150 patients with massive or submassive PE using an EKOS® and lytic combination, the mean RV/LV ratio decreased from 1.55 pre-procedure to 1.13 at 48 hours post-procedure (P<0.0001) while PA systolic pressure decreased from 51.4mmHg to 36.9mmHg (P<0.0001).*

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

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

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

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