Celebrating 10 Years
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COURTESY YU KWAN LEE/CLEVELAND CLINIC

Cleveland Clinic's PERT mobilizes specialists' expertise to treat patients with submassive and massive pulmonary embolisms.

The Cleveland Clinic PERT's first outcomes

BY KATIE WAGNER LENNON
Frontline Medical News

AT CHEST 2016

LOS ANGELES – Initial outcomes measures are beginning to emerge from Pulmonary Embolism Response Teams (PERT).

Members of the Cleveland Clinic's PERT, which was established in 2014, presented some of their preliminary data during a presentation at the CHEST annual meeting.

Their findings indicate that "our residents, staff, and clinicians [understand] the utility of the PERT team and when and how to activate it. We have [documented that our approaches have] been associated with overall low bleeding risks," study presenter Jamal Mahar, MD, said in an interview.

The concept behind the PERT is to rapidly mobilize a team with varied expertise helpful for treating patients with pulmonary embolisms (PEs). While the PERT "can be activated by any (clinician) for any patient, even low-risk patients ... those with submassive and massive PEs [intermediate- and high-risk patients]" are the target patients, said Dr. Mahar of the Cleveland Clinic.

The first PERT was created at Massachusetts General Hospital in Boston in 2012, according to the National

See **PERT** • *page 4*

Survey participants given a voice in MOC exam content

Responses could improve exam quality.

BY MICHAEL E. NELSON, MD, FCCP, AND THE ABIM PULMONARY MEDICINE BOARD

The American Board of Internal Medicine (ABIM) has emailed diplomates a survey regarding the blueprint for the Maintenance of Certification (MOC) pulmonary exam.

This survey relates to the content of the exam, as opposed to a prior survey that asked diplomates for their opinion about new proposals for 2- and 5-year cycles for the exam. Participating in the survey gives diplomates a voice in determining the content of the MOC exam for pulmonary medicine. If enough individuals participate in the survey and the data support changing the distribution of exam content, it is very likely that ABIM will make improvements to the MOC exam.

The figure on page 24 illustrates the information provided by diplomates that ABIM used to help them decide the exam content for the Hospital Medicine exam.

ABIM has heard from practicing physicians and the specialty societies about the need to change MOC

See **MOC** • *page 24*

INSIDE

New mechanical ventilation protocols

BY DOUG BRUNK
Frontline Medical News

AT CHEST 2016

LOS ANGELES – Acutely hospitalized patients who have been on mechanical ventilation for more than 24 hours, are at high risk for extubation failure, and have passed a spontaneous breathing trial should be extubated to noninvasive ventilation.

The recommendation comes from new clinical practice guidelines from the American College of Chest Physicians and the American Thoracic Society. Moderate-quality evidence suggests that early extubation and a switch to noninvasive ventilation reduces ventilator- and ICU-related complications, including infections and injury to the lungs and other organs. Extubation also cuts costs by reducing ICU stays.

Conditional recommendations are to use inspiratory pressure augmentation during the initial spontaneous breathing trial and to employ protocols to mini-

See **New protocols** • *page 8*

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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.

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

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Team review expedites decisions

PERT *from page 1*

Consortium of Pulmonary Embolism Response Team's website.

As of May 2015, the PERT model has been adopted by physicians and health care professionals from more than 40 institutions.

Dr. Mahar reported that the Cleveland Clinic's PERT is activated through a single pager that resides with a vascular medicine fellow during the day and a critical care fellow at night. When paged, the fellow promptly evaluates the patient and ensures a complete basic work-up, which includes an ECG, cardiac enzymes, N-terminal pro b-type natriuretic peptide, lower-extremity deep vein thrombosis scans, transthoracic echocardiogram, and confirmatory CT/PE protocol or ventilation/perfusion scan.

Based on the simplified Pulmonary Embolism Severity Index and Bova scores, the patient is risk stratified and the patient's indications, and relative and absolute contraindications to advanced therapies are reviewed. The fellow next sends a

group notification to the PERT via email and text message. The team then convenes online for a virtual meeting and case presentation that includes sharing of lab and test results and images.

The process sounds complex, but the surgeon, interventional radiologist, vascular medicine specialist, and cardiologist are on call and simultaneously get the message and respond, Dr. Mahar said. With a team approach, the decision to use advanced therapies – systemic lytics, surgery, catheter-directed lysis and extracorporeal membrane oxygenation – is expedited. "For example, over the last 2 years, four out of four patients who underwent surgical embolectomies had good outcomes without any deaths," he said.

Based on a retrospective chart review from October 2014 through August 2016, Cleveland Clinic's PERT had been activated for 134 patients, 112 of whom were found to have PEs, Dr. Mahar said during his presentation at the annual meeting of the American College of Chest Physicians (CHEST).

The number of low risk, submassive, and massive PEs were 14 (12%), 76 (68%), and 22 (20%), respectively. Just over half of the PE patients, 55% (60 patients), were treated with anticoagulation therapy alone. Inferior vena cava filters were placed in 32 patients (29%); 14 patients received catheter-directed thrombolysis, 3 received a suction thrombectomy, and 4 received a surgical embolectomy.

DR. JAMAL MAHAR

Patients with submassive and massive PEs are the targets, Dr. Mahar said.

The 30-day all-cause mortality rate was 9%; the deaths occurred in six patients who had massive PEs, three patients with submassive PEs, and one patient with a low-risk PE. Six of the patients who died had been treated with anticoagulation, two had received catheter-directed thrombolysis, and one had received a full dose of systemic thrombolysis.

Bleeding complications occurred in 10 patients, 6 of whom were treated with anticoagulation alone and 4 of whom underwent catheter-directed thrombolysis.

Cleveland Clinic is a large entity with multiple resources, but the principles of PERT can be applied in smaller facilities, as well, according to Gustavo A. Heresi-Davila, MD, medical director of the Cleveland Clinic's pulmonary thromboendarterectomy program and the lead researcher for the PERT project at the clinic. "I would emphasize the notion that a PERT has to be multidisciplinary, as people with different backgrounds and expertise bring complementary talent to the discus-

Continued on following page

Continued from previous page

sion of each case. I would not minimize the challenges of assembling such a team," he said during an interview following the meeting.

The moderator of the meeting session, Robert Schilz, DO, PhD, noted, that the goal of PERT is to determine the best approach for an individual patient based on available resources.

To establish a PERT, "you don't have to be able to put a patient on ECMO [extracorporeal membrane oxygenation] in 15 minutes, and you don't have to be able to do endarterectomies, embolectomies, and all the catheter-drive techniques emergently. But you do need to have the disposition to have efficient and standardized care, and the solutions may need to be very geographic. What hospital A may do may be very different from hospital B."

Small hospitals can draw on their available resources, added Dr. Schilz, director of pulmonary vascular disease and lung transplantation at Case Western Reserve University, Cleveland. "Most hospitals have cardiologists on call 24/7, and many have some flavor of interventional radiology; others have clear referral and transfer schemes. Emergency department personnel at small rural hospitals can rapidly identify patients appropriate for transfer."

Dr. Mahar added that PERTs are already being utilized in smaller hospitals and that he thinks that, in the next 5 years, having a PERT will be the standard protocol.

Dr. Mahar had no disclosures.

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Mary Jo M. Dales contributed to this report.

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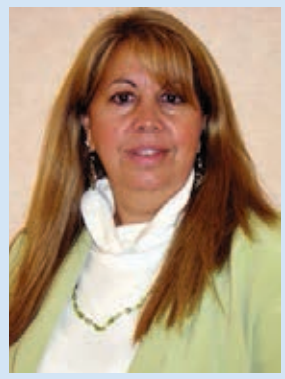

Vera A. De Palo, MD, MBA, FCCP, is Medical Editor in Chief of CHEST Physician.

NIV failure not reduced with He/O_2 in COPD patients

BY BOB KIRSCH
Frontline Medical News

Inhaling He/O_2 did not result in a lower NIV failure rate than inhaling Air/O_2 in COPD patients requiring noninvasive ventilation, in a randomized, controlled study.

In the study, known as the E.C.H.O. ICU trial, patients either received $He/0_2$ (a 78%/22% mixture blended with 100% O_2) or a conventional Air/O_2 mixture for up to 72 hours, during both noninvasive ventilation (NIV) and spontaneous breathing.

Previous research had demonstrated that during hypercapnic COPD exacerbations, the He/O_2 mixture reduces airway resistance, partial pressure of carbon dioxide in arterial blood ($PaCO_2$), intrinsic positive end-expiratory pressure, and work of breathing during both spontaneous breathing and NIV, compared with Air/O_2, said Philippe Jolliet, MD, and his colleagues.

Correction
On page 26 of the November issue of CHEST Physician, the headline was incorrect. The headline should have read "Surgical lung biopsies are unnecessary for most ILDs."

The two treatment groups in the E.C.H.O. ICU trial had similar NIV failure rates – defined as endotracheal intubation or death without intubation. The rates were 14.7% for the patients who received He/O_2 and 14.5% for the patients who received Air/O_2. The NIV failures for 31 of the patients in the He/O_2 group resulted in intubation; the remaining two patients who were classified as having NIV failure died. All 32 of the patients in the Air/O_2 group who had NIV failures were intubated.

The length of ICU stay was also comparable between the two groups. In the subgroups of patients with severe acidosis (having a pH of less than 7.30) from both the He/O_2 and Air/O_2 groups, the NIV failure rates were again nearly identical (AJRCCM. 2016 Oct 13; doi: 10.1164/rccm.201601-0083OC).

The average times to NIV failure were 93 hours in the He/O_2 group (N = 33) and 52 hours in the Air/O_2 group (N = 32, $P = .12$). The He/O_2 group achieved a significantly quicker improvement in respiratory acidosis, encephalopathy score, and respiratory rate.

Patients intubated following an NIV failure who had received He/O_2 had a shorter ventilation duration and a shorter ICU stay than

Continued on following page

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Continued from previous page

did the intubated patients who had received Air/O_2 (7.4 days, vs. 13.6 days, $P = .02$, and 15.8 vs. 26.7 days, $P = .01$).

No significant differences appeared in the safety profile of the two groups, nor were significant differences seen in ICU, hospital, or 6-month mortality rates; or in 6-month hospital readmission rates.

"[The] study was stopped prematurely after a futility analysis due to the low event rate identified by [an independent adjudication committee]," said Dr. Jolliet of the intensive care and burn unit at Le Centre Hospitalier Universitaire Vaudois (CHUV), in Lausanne, Switzerland, and his fellow researchers.

The study included 445 patients from ICUs or intermediate care units in six countries. The inclusion criteria were presenting with current COPD exacerbation with hypercapnic acute respiratory failure, a $PaCO_2$ of at least 45 mm Hg, an arterial pH of less than or equal to 7.35, and at least one of the following: respiration rate of at least 25 breaths per minute, a PaO_2 less than or equal to 50 mm Hg, and an arterial oxygen saturation of less than or equal to 90%.

Half of the patients in each group were already receiving NIV prior to enrollment in the study. Males constituted two thirds of all enrolled patients.

Patients intubated following an NIV failure who had received He/O_2 had a shorter ventilation duration and a shorter ICU stay than did the intubated patients who had received Air/O_2.

HeO_2 administration was limited to 72 hours for each patient and about a third of NIV failures occurred after the end of the HeO_2 administration, the researchers said.

"The main reason for the absence of observed benefit on outcome in the He/O_2 probably lies in the very low NIV failure rate now observed in both groups. One possible mechanism explaining the low intubation rate could be that some patients had received uncontrolled oxygen therapy prior to ICU admission, thereby worsening initial hypercapnia and acidosis, a problem that can easily be corrected by adequate titration," the researchers said. "The 14.5% failure rate in the Air/O_2 group was much lower than the 25% rate used in designing the study," which was based on previous research.

The trial's sponsor, Air Liquide Healthcare, provided input into the design and conduct of the study; oversaw the collection, management, and statistical analysis of data; and contributed to the manuscript's preparation and review.

Empirical micafungin failed to boost survival of ICU sepsis

BY SUSAN LONDON
Frontline Medical News

MILAN – Empirical antifungal treatment did not improve the rate of survival free of invasive fungal infection among high-risk colonized patients in the intensive care unit, based on results from the EMPIRICUS randomized controlled trial.

Trial participants were 260 nonneutropenic, nontransplanted critically ill patients with ICU-acquired sepsis, *Candida* colonization of at least one site, and multiple organ failure who were exposed to broad-spectrum antibacterial agents. They were randomized to 14 days of empirical treatment with micafungin (Mycamine, 100 mg once daily) or placebo.

By day 28, about two-thirds of patients overall remained alive and free of proven invasive fungal infection, with no significant difference between groups, according to data reported at the annual congress of the European Society of Intensive Care Medicine and simultaneously published online (JAMA. 2016 Oct 5. doi: 10.1001/jama.2016.14655). Results were similar in subsets of patients having established risk factors for candidemia.

The EMPIRICUS (Empirical Antifungal Treatment in ICUs) findings add to data from other studies suggesting that, in this patient population, sepsis is seldom a result of invasive fungal infection and *Candida* colonization status is not helpful for guiding treatment, according to the researchers, who were led by Dr. Jean-Francois Timsit of Inserm/Paris Diderot University and department of medical intensive care and infectious diseases, Hôpital Bichat-Claude-Bernard, Paris.

"Altogether, these results call into question the routine use of systematic surveillance for *Candida* colonization. Besides sparing unnecessary use of health care resources, it may also avoid inducing resistances to antifungals," they maintain. "Whether this trial closes 3 decades of clinical research on *Candida* colonization deserves consideration."

Patients were recruited to EMPIRICUS from 19 ICUs in France. On average, study participants had three *Candida*-colonized sites.

A modified intent-to-treat analysis showed that, by day 28 after enrollment, 68% of patients in the micafungin group and 60.2% in the placebo group were alive and free of invasive fungal infection, a nonsignificant difference.

Findings were similar in the subset of patients having high serum levels of (1-3)-beta-D-glucan and in the subset of patients having high Sequential Organ Failure Assessment (SOFA) scores – both risk factors for candidemia – and regardless of the number of colonized sites.

In analyses of secondary outcomes, empirical micafungin was associated with a lower rate of new invasive fungal infection when compared with placebo (3% vs. 12%; $P = .008$), but the rate of mortality was statistically indistinguishable (30.0% vs. 29.7%).

The groups were statistically indistinguishable with respect to the number of organ failure–free days and the rate of ventilator-acquired pneumonia.

Dr. Timsit disclosed that he receives lecture fees from Gilead, Pfizer, Merck, and Astellas; research grants to his university and research organization from Astellas, Gilead, Merck, and Pfizer companies; a consultancy honorarium from Bayer; and personal fees from Abbott for scientific board participation; additionally, he disclosed participation on a scientific committee of epidemiological studies organized by Astellas and Merck companies outside the submitted work. Astellas provided a research grant to the Grenoble Alpes University Hospital based on the final study protocol. The study was sponsored by the University of Grenoble 1/Albert Michallon University Hospital.

The University of Grenoble provided compensation to the participating hospitals and universities for extra costs associated with the study.

VIEW ON THE NEWS

It's time to revisit guidelines endorsing empirical antifungal therapy

Taken together, findings from EMPIRICUS and similar trials suggest that empirical antifungal treatment may reduce rates of invasive infection in critically ill patients, but does not improve survival.

These findings highlight two emerging themes in critical care medicine – less is more and targeted therapies are important when treating invasive fungal infection. In particular, the safety and efficacy of the newer antifungal agents are driving greater empirical use, yet this practice increases the cost of care and may contribute to antifungal resistance.

Guidelines have been implemented for empirical treatment of *Candida* and serial surveillance, yet there are no conclusive mortality benefits for this approach. Data have not ruled out the possibility that some subgroups of patients may see a survival benefit but, in light of the situation, guidelines concerning empirical treatment and surveillance should be revisited.

Like other prophylactic interventions, the risks and potential benefits of empirical echinocandin therapy for critically ill, immunocompetent patients in the ICU need to be studied. Novel biomarkers or clinical risk assessment algorithms may help in identifying those patients who are at highest risk of infection-related morbidity and mortality and would benefit most from targeted preventive therapies.

Trishul Siddharthan, MD, Petros C. Karakousis, MD, and William Checkley, MD, PhD, are with Johns Hopkins University in Baltimore. They made their remarks in an accompanying editorial in JAMA (2016 Oct 5. doi: 10.1001/jama.2016.13801).

CHEST recommends new protocols

New protocols *from page 1*

mize sedation in patients ventilated for more than 24 hours.

At the annual meeting of the American College of Chest Physicians, one of the six project cochairs, Daniel R. Ouellette, MD, said that the guidelines were intended to address "new territory" from the evidence-based guidelines for weaning and discontinuing ventilator support that were published in 2001.

That effort, chaired by Neil R. MacIntyre, MD, "was a landmark article that helped us learn about the steps that we needed to take to liberate patients from mechanical ventilation," said Dr. Ouellette of the Henry Ford Hospital department of pulmonary and critical care medicine, Detroit. "We hope that this guideline lives up to the importance of that one. We wanted to look over new information and give new recommendations about things that haven't been addressed in the past."

Six recommendations from the guideline panel include:

We suggest that the initial spontaneous breathing trial be conducted with inspiratory pressure augmentation rather than T-piece or continuous positive airway pressure. The committee wrote that conducting the initial spontaneous breathing trial with pressure augmentation was more likely to be successful, produced a higher rate of extubation success, and was associated with a trend toward lower ICU mortality.

We suggest protocols attempting to minimize sedation. The committee found that sedation protocols reduced ICU length of stay. However, the protocols did not appear to decrease time on the ventilator or reduce short-term mortality. The authors could not recommend one protocol over another but said the burden of providing sedation by any of the protocols was "very low."

We suggest protocolized rehabilitation directed toward early mobilization. The committee wrote that patients receiving the intervention spent less time on the ventilator and were more likely to be able to walk when they left the hospital. However, their mortality rate appeared unchanged. The authors noted the exercises created additional work for ICU staff that might have come at the expense of other care priorities.

We suggest managing patients with a ventilator liberation protocol. The committee said that patients managed by protocol spent on average 25 fewer hours on mechanical ventilation and were discharged from the ICU a day early. However, their mortality rate appeared unchanged.

The guidelines were intended to address "new territory" from the evidence-based guidelines for weaning and discontinuing ventilator support that were published in 2001.

We suggest performing a cuff leak test in patients who meet extubation criteria and are deemed at high risk for postextubation stridor. The committee suggested that the test should be used only in patients with a high risk of stridor (abnormal breathing caused by blockage of windpipe) after extubation. Although patients passing the test had lower stridor and reintubation rates, the authors wrote that a high percentage of patients who failed the test could be successfully extubated.

For patients who failed the cuff leak test but are otherwise ready for extubation, we suggest administering systemic steroids at least 4 hours before extubation. The committee said that clinical judgment should take priority over test results, and systemic steroids should be administered to these patients at least 4 hours before extubation. The authors added that the short duration of the steroid therapy was likely to improve success rates without resulting in adverse events.

In a prepared statement, Timothy Girard, MD, of the department of medicine at the University of Pittsburgh and a lead author of the guidelines said the committee hoped the guidelines would help reduce variations in practice that do not benefit patients. "We are not prescribing a specific approach to care for every patient every time," he said. "But we are trying to summarize the available evidence in as clear and succinct a way as possible so that clinicians know how it applies to most patients."

Dr. Ouellette disclosed that he has received a research grant from Cardeas Pharma for health care–associated pneumonia.

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VIEW ON THE NEWS

Daniel R. Ouellette, MD, FCCP, comments:

Liberation from mechanical ventilation is one of the most important goals in taking care of critically ill patients receiving mechanical ventilation in the ICU. Patients who have a prolonged ventilator course are at risk for many complications and so physicians who work in the intensive care unit must work carefully to liberate patients from the ventilator at the earliest possible moment. That has to be done in a safe fashion so criteria to ensure that this can be done safely are important as well.

Patients often have medical illness that requires sedation, and it is often necessary to sedate patients so that they can tolerate being on mechanical ventilation; however, we know that oversedation can lead to failure to liberate patients from mechanical ventilation expeditiously. Therefore, one of our recommendations' suggestions is to design protocols for sedation that focus on minimizing sedation so that patients can be extubated expeditiously.

All of the recommendations ultimately focused on a team approach to liberation from mechanical ventilation, because involvement of team members is always important. However, there are a couple of our recommendations that are particularly important in terms of their implications for the team approach and those include recommendations about using protocols to liberate patients from ventilators, in general, and also to use sedation protocols to minimize sedations.

We began to look at developing this topic, because we had initially published guidelines on [liberation from mechanical ventilation] in 2001. We knew that there was much new information that had emerged since the 2001 guidelines. For that reason we began to think about an update. With the initial inception of this project, we reached out to the American Thoracic Society so as to develop a collaborative effort since this was a topic that interested both societies. This collaboration was at all levels at CHEST and it involved not only the guidelines organization, but also the leadership of both societies and, of course, the panel that was ultimately constructed to address these issues was made up of members from both societies. The entire process [of developing the new guideline] took nearly 3 years.

When one develops a guideline, one makes an effort to make a guideline as comprehensive and globally applicable as possible. I think the practices in Europe are very similar to practices in North America in terms of mechanical ventilation. Several of our panelists are European and some of the important work that we reviewed came from centers in Europe. It's my opinion that our guideline will be broadly applicable in both North America and Europe, but there may be regional or local differences. Nevertheless, we recognize in different regions in the world, there are different resource allocations for medical treatment, there are different cultural precepts, and there are other factors that implicate medical problems.

Certainly the European Respiratory Society and other European organizations developed guidelines on related topics ... one of the important caveats when CHEST decides to develop a guideline is that we are not reproducing the work that has been done elsewhere and so this guideline represents a project that fills a gap that previously had not been filled.

All guidelines that CHEST develops are living guidelines … it's hard to envision exactly how often a guideline will be updated. We know that there will be certain areas of our guideline that will stand the test of time, but there will be other areas that will need to be updated, some sooner than others.

The original CHEST guideline on liberation from mechanical ventilation was a very important document that appeared in 2001 and changed the practice of medicine and the practice of managing patients on mechanical ventilation. Nevertheless, the guideline was somewhat limited in scope, because there was only so much information available. … Our goal in developing this guideline was to address some of practitioners' questions that had emerged in the last decade by looking at newly available data.

[In formulating these guidelines], we purposely chose six new questions that were not directly related to any of the questions [that has been answered] in the previous guideline.

The power of flexibility is yours with **REVATIO Oral Suspension**

With REVATIO you have 3 dosage forms to treat pulmonary arterial hypertension (PAH): oral suspension, tablet, and injection.

Choose your dosage form based on each patient's needs.

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Indication

REVATIO is a phosphodiesterase-5 (PDE-5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) in adults to improve exercise ability and delay clinical worsening. Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominately patients with NYHA Functional Class II-III symptoms. Etiologies were idiopathic (71%) or associated with connective tissue disease (25%).

Limitation of Use: Adding sildenafil to bosentan therapy does not result in any beneficial effect on exercise capacity.

Important Safety Information

REVATIO is contraindicated in patients with concomitant use of organic nitrates in any form, either regularly or intermittently, because of the greater risk of hypotension.

REVATIO is contraindicated in patients with concomitant use of riociguat, a soluble guanylate cyclase (sGC) stimulator medication. PDE5 inhibitors, including sildenafil, may potentiate the hypotensive effects of riociguat.

REVATIO is contraindicated in patients with a known hypersensitivity to sildenafil or any other ingredient in REVATIO. Hypersensitivity, including anaphylactic reaction, anaphylactic shock, and anaphylactoid reaction has been reported in association with the use of sildenafil.

Use of REVATIO, particularly chronic use, is not recommended in children.

Before starting REVATIO, physicians should carefully consider whether their patients with underlying conditions could be adversely affected by the mild and transient vasodilatory effects of REVATIO on blood pressure. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD) and administration of REVATIO to these patients is not recommended. Should signs of pulmonary edema occur when sildenafil is administered, the possibility of associated PVOD should be considered.

Caution is advised when PDE5 inhibitors, such as REVATIO, are administered with α–blockers as both are vasodilators with blood pressure lowering effects.

In PAH patients, the concomitant use of vitamin K antagonists and REVATIO resulted in a greater incidence of reports of bleeding (primarily epistaxis) versus placebo. The incidence of epistaxis was higher in patients with PAH secondary to CTD (sildenafil 13%, placebo 0%) than in PPH patients (sildenafil 3%, placebo 2%).

Co-administration of REVATIO with potent CYP3A4 inhibitors (eg, ketoconazole, itraconazole, and ritonavir) is not recommended as serum concentrations of sildenafil substantially increase. Co-administration of REVATIO with potent CYP3A4 inducers such as barbiturates, carbamazepine, phenytoin, efavirenz, nevirapine, rifampin, and rifabutin, is expected to cause substantial decreases in plasma levels of sildenafil. Treatment with doses higher than 20 mg three times a day is not recommended.

Non-arteritic anterior ischemic optic neuropathy (NAION) has been reported post-marketing in temporal association with the use of PDE5 inhibitors for the treatment of erectile dysfunction, including sildenafil. Physicians should advise patients to seek immediate medical attention in the event of sudden loss of vision while taking PDE5 inhibitors, including REVATIO. Physicians should also discuss the increased risk of NAION with patients who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE-5 inhibitors.

Sudden decrease or loss of hearing has been reported in temporal association with the intake of PDE5 inhibitors, including REVATIO. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE5 inhibitors, including REVATIO.

REVATIO should be used with caution in patients with anatomical deformation of the penis or patients who have conditions which may predispose them to priapism.

The effectiveness of REVATIO in pulmonary hypertension (PH) secondary to sickle cell anemia has not been established. In a small, prematurely terminated study of patients with PH secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported by patients who received REVATIO than by those randomized to placebo.

Patients with retinitis pigmentosa and patients on bosentan did not participate in the preapproval clinical trial. The safety of REVATIO is unknown in patients with bleeding disorders and patients with active peptic ulceration. In these patients, physicians should prescribe REVATIO with caution.

REVATIO contains sildenafil, the same active ingredient found in VIAGRA®. Combinations of REVATIO with VIAGRA or other PDE5 inhibitors have not been studied. Patients taking REVATIO should not take VIAGRA or other PDE5 inhibitors.

The most common side effects of REVATIO (placebo-subtracted) were epistaxis (8%), headache (7%), dyspepsia (6%), flushing (6%), and insomnia (6%). Adverse events were generally transient and mild to moderate. Adverse events of REVATIO injection were similar to those seen with oral tablets.

The most common side effects of REVATIO (placebo-subtracted) as an adjunct to intravenous epoprostenol were headache (23%), edema (14%), dyspepsia (14%), pain in extremity (11%), diarrhea (7%), nausea (7%), and nasal congestion (7%).

At doses higher than the recommended 20 mg TID, there was a greater incidence of some adverse events including flushing, diarrhea, myalgia, and visual disturbances.

No dose adjustment required for renal impaired.

No dose adjustment required for mild to moderate hepatic impaired. Severe impairment has not been studied.

REVATIO is available in the following dosage forms:

- Tablets: 20 mg
- Injection: 10 mg/12.5 mL in a single use vial
- Oral Suspension: 10 mg/mL (when reconstituted)

The Revatio® Family

Available in OS, tablet, and injection forms.

Please see brief summary of Full Prescribing Information on following pages.

Revatio® sildenafil

PP-REV-USA-0090-01

July 2016

Revatio® sildenafil 20 mg tablets

Brief Summary of Prescribing Information. Consult Full Prescribing Information at REVATIOHCP.com

INDICATION AND USAGE

REVATIO is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in adults to improve exercise ability and delay clinical worsening. The delay in clinical worsening was demonstrated when REVATIO was added to background epoprostenol therapy.

Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominately patients with New York Heart Association (NYHA) Functional Class II-III symptoms and idiopathic etiology (71%) or associated with connective tissue disease (CTD) (25%).

Limitation of Use: Adding sildenafil to bosentan therapy does not result in any beneficial effect on exercise capacity.

DOSAGE AND ADMINISTRATION

REVATIO Tablets and Oral Suspension The recommended dose of REVATIO is 5 mg or 20 mg three times a day. Administer REVATIO doses 4–6 hours apart. In the clinical trial no greater efficacy was achieved with the use of higher doses. Treatment with doses higher than 20 mg three times a day is not recommended.

Reconstitution of the Powder for Oral Suspension 1. Tap the bottle to release the powder. 2. Remove the cap. 3. Accurately measure out 60 mL of water and pour the water into the bottle. 4. Replace the cap and shake the bottle vigorously for a minimum of 30 seconds. 5. Remove the cap. 6. Accurately measure out another 30 mL of water and add this to the bottle. You should always add a total of 90 mL of water irrespective of the dose prescribed. 7. Replace the cap and shake the bottle vigorously for a minimum of 30 seconds. 8. Remove the cap. 9. Press the bottle adaptor into the neck of the bottle. The adaptor is provided so that you can fill the oral syringe with medicine from the bottle. Replace the cap on the bottle. 10. Write the expiration date of the constituted oral suspension on the bottle label (the expiration date of the constituted oral suspension is 60 days from the date of constitution).

Incompatibilities Do not mix with any other medication or additional flavoring agent.

CONTRAINDICATIONS

REVATIO is contraindicated in patients with concomitant use of organic nitrates in any form, either regularly or intermittently, because of the greater risk of hypotension *[see Warnings and Precautions]*, Concomitant use of riociguat, a guanylate cyclase stimulator. PDE5 inhibitors, including sildenafil, may potentiate the hypotensive effects of riociguat. REVATIO is also contraindicated in patients with known hypersensitivity to sildenafil or any component of the tablet, injection, or oral suspension. Hypersensitivity, including anaphylactic reaction, anaphylactic shock and anaphylactoid reaction, has been reported in association with the use of sildenafil.

WARNINGS AND PRECAUTIONS

Mortality with Pediatric Use In a long-term trial in pediatric patients with PAH, an increase in mortality with increasing REVATIO dose was observed. Deaths were first observed after about 1 year and causes of death were typical of patients with PAH. Use of REVATIO, particularly chronic use, is not recommended in children *[see Use in Specific Populations]*.

Hypotension REVATIO has vasodilatory properties, resulting in mild and transient decreases in blood pressure. Before prescribing REVATIO, carefully consider whether patients with certain underlying conditions could be adversely affected by such vasodilatory effects (e.g., patients on antihypertensive therapy or with resting hypotension [BP less than 90/50], fluid depletion, severe left ventricular outflow obstruction, or automatic dysfunction). Monitor blood pressure when co-administering blood pressure lowering drugs with REVATIO.

Worsening Pulmonary Vascular Occlusive Disease Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Since there are no clinical data on administration of REVATIO to patients with veno-occlusive disease, administration of REVATIO to such patients is not recommended. Should signs of pulmonary edema occur when REVATIO is administered, consider the possibility of associated PVOD.

Epistaxis The incidence of epistaxis was 13% in patients taking REVATIO with PAH secondary to CTD. This effect was not seen in idiopathic PAH (REVATIO 3%, placebo 2%) patients. The incidence of epistaxis was also higher in REVATIO-treated patients with a concomitant oral vitamin K antagonist (9% versus 2% in those not treated with concomitant vitamin K antagonist). The safety of REVATIO is unknown in patients with bleeding disorders or active peptic ulceration.

Visual Loss When used to treat erectile dysfunction, non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported postmarketing in temporal association with the use of phosphodiesterase type 5 (PDE-5) inhibitors, including sildenafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. Based on published literature, the annual incidence of NAION is 2.5–11.8 cases per 100,000 males aged ≥ 50 per year in the general population. An observational study evaluated whether recent, episodic use of PDE5 inhibitors (as a class), typical of erectile dysfunction treatment, was associated with acute onset of NAION. The results suggest an approximately 2-fold increase in the risk of NAION within 5 half-lives of PDE5 inhibitor use. It is not possible to determine whether these events are related directly to the use of PDE-5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors. Advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking PDE-5 inhibitors, including REVATIO. Physicians should also discuss the increased risk of NAION with patients who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE-5 inhibitors.

There are no controlled clinical data on the safety or efficacy of REVATIO in patients with retinitis pigmentosa, a minority whom have genetic disorders of retinal phosphodiesterases. Prescribe REVATIO with caution in these patients.

Hearing Loss Cases of sudden decrease or loss of hearing, which may be accompanied by tinnitus and dizziness, have been reported in temporal association with the use of PDE-5 inhibitors, including REVATIO. In some of the cases, medical conditions and other factors were reported that may have played a role. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of REVATIO, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors. Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE-5 inhibitors, including REVATIO.

Combination with Other PDE-5 Inhibitors Sildenafil is also marketed as VIAGRA®. The safety and efficacy of combinations of REVATIO with VIAGRA or other PDE-5 inhibitors have not been studied. Inform patients taking REVATIO not to take VIAGRA or other PDE-5 inhibitors.

Priapism Use REVATIO with caution in patients with anatomical deformation of the penis (e.g., angulation, cavernosal fibrosis, or Peyronie's disease) or in patients who have conditions, which may predispose them to priapism (e.g., sickle cell anemia, multiple myeloma, or leukemia). In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism (painful erection greater than 6 hours in duration) is not treated immediately, penile tissue damage and permanent loss of potency could result.

Vaso-occlusive Crisis in Patients with Pulmonary Hypertension Secondary to Sickle Cell Anemia In a small, prematurely terminated study of patients with pulmonary hypertension (PH) secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported by patients who received REVATIO than by those randomized to placebo. The effectiveness and safety of REVATIO in the treatment of PAH secondary to sickle cell anemia has not been established.

ADVERSE REACTIONS

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

Safety data of REVATIO in adults were obtained from the 12-week, placebo-controlled clinical study (Study 1) and an open-label extension study in 277 REVATIO-treated patients with PAH, WHO Group I.

The overall frequency of discontinuation in REVATIO-treated patients on 20 mg three times a day was 3% and was the same for the placebo group. In Study 1, the adverse reactions that were reported by at least 3% of REVATIO-treated patients (20 mg three times a day) and were more frequent in REVATIO-treated patients than in placebo-treated patients are shown in Table 1. Adverse reactions were generally transient and mild to moderate in nature.

Table 1: Most Common Adverse Reactions in Patients with PAH in Study 1 (More Frequent in REVATIO-Treated Patients than Placebo-Treated Patients and Incidence ≥3% in REVATIO-Treated Patients)

	Placebo, % (n=70)	REVATIO 20 mg three times a day, % (n=69)	Placebo-Subtracted, %
Epistaxis	1	9	8
Headache	39	46	7
Dyspepsia	7	13	6
Flushing	4	10	6
Insomnia	1	7	6
Erythema	1	6	5
Dyspnea exacerbated	3	7	4
Rhinitis	0	4	4
Diarrhea	6	9	3
Myalgia	4	7	3
Pyrexia	3	6	3
Gastritis	0	3	3
Sinusitis	0	3	3
Paresthesia	0	3	3

At doses higher than the recommended 20 mg three times a day, there was a greater incidence of some adverse reactions including flushing, diarrhea, myalgia and visual disturbances. Visual disturbances were identified as mild and transient, and were predominately color-tinge to vision, but also increased sensitivity to light or blurred vision.

The incidence of retinal hemorrhage with REVATIO 20 mg three times a day was 1.4% versus 0% placebo and for all REVATIO doses studied was 1.9% versus 0% placebo. The incidence of eye hemorrhage at both 20 mg three times a day and at all doses studied was 1.4% for REVATIO versus 1.4% for placebo. The patients experiencing these reactions had risk factors for hemorrhage including concurrent anticoagulant therapy.

Postmarketing Experience The following adverse reactions have been identified during post approval use of sildenafil (marketed for both PAH and erectile dysfunction). 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.

Cardiovascular Events In postmarketing experience with sildenafil at doses indicated for erectile dysfunction, serious cardiovascular, cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, pulmonary hemorrhage, and subarachnoid and intracerebral hemorrhages have been reported in temporal association with the use of the drug. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of sildenafil without sexual activity. Others were reported to have occurred hours to days after use concurrent with sexual activity. It is not possible to determine whether these events are related directly to sildenafil, to sexual activity, to the patient's underlying cardiovascular disease, or to a combination of these or other factors.

Nervous system Seizure, seizure recurrence.

DRUG INTERACTIONS

Nitrates Concomitant use of REVATIO with nitrates in any form is contraindicated *[see Contraindications]*.

Ritonavir and other Potent CYP3A Inhibitors Concomitant use of REVATIO with ritonavir and other potent CYP3A inhibitors is not recommended.

Other drugs that reduce blood pressure *Alpha blockers.* In drug-drug interaction studies, sildenafil (25 mg, 50 mg, or 100 mg) and the alpha-blocker doxazosin (4 mg or 8 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on doxazosin therapy. In these study populations, mean additional reductions of supine systolic and diastolic blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, respectively, were observed. Mean additional reductions of standing blood pressure of 6/6 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively, were also observed. There were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and light-headedness, but not syncope.

Amlodipine. When sildenafil 100 mg oral was co-administered with amlodipine, 5 mg or 10 mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was 8 mmHg systolic and 7 mmHg diastolic.

Monitor blood pressure when co-administering blood pressure lowering drugs with REVATIO® (sildenafil).

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B There are no adequate and well-controlled studies of sildenafil in pregnant women. No evidence of teratogenicity, embryotoxicity, or fetotoxicity was observed in pregnant rats or rabbits dosed with sildenafil 200 mg/kg/day during organogenesis, a level that is, on a mg/m^2 basis, 32- and 68-times, respectively, the recommended human dose (RHD) of 20 mg three times a day. In a rat pre- and postnatal development study, the no-observed-adverse-effect dose was 30 mg/kg/day (equivalent to 5-times the RHD on a mg/m^2 basis).

Labor and Delivery The safety and efficacy of REVATIO during labor and delivery have not been studied.

Nursing Mothers It is not known if sildenafil or its metabolites are excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when REVATIO is administered to a nursing woman.

Pediatric Use In a randomized, double-blind, multi-center, placebo-controlled, parallel-group, dose-ranging study, 234 patients with PAH, aged 1 to 17 years, body weight greater than or equal to 8 kg, were randomized, on the basis of body weight, to three dose levels of REVATIO, or placebo, for 16 weeks of treatment. Most patients had mild to moderate symptoms at baseline: WHO Functional Class I (32%), II (51%), III (15%), or IV (0.4%). One-third of patients had primary PAH; two-thirds had secondary PAH (systemic-to-pulmonary shunt in 37%; surgical repair in 30%). Sixty-two percent of patients were female. Drug or placebo was administered three times a day.

The primary objective of the study was to assess the effect of REVATIO on exercise capacity as measured by cardiopulmonary exercise testing in pediatric patients developmentally able to perform the test (n=115). Administration of REVATIO did not result in a statistically significant improvement in exercise capacity in those patients. No patients died during the 16-week controlled study.

After completing the 16-week controlled study, a patient originally randomized to REVATIO remained on his/her dose of REVATIO or, if originally randomized to placebo, was randomized to low-, medium-, or high-dose REVATIO. After all patients completed 16 weeks of follow-up in the controlled study, the blind was broken and doses were adjusted as clinically indicated. Patients treated with sildenafil were followed for a median of 4.6 years (range 2 days to 8.6 years). During the study, there were 42 reported deaths, with 37 of these deaths reported prior to a decision to titrate subjects to a lower dosage because of a finding of increased mortality with increasing REVATIO doses. For the survival analysis which included 37 deaths, the hazard ratio for high dose compared to low dose was 3.9, p=0.007. Causes of death were typical of patients with PAH. Use of REVATIO, particularly chronic use, is not recommended in children.

Geriatric Use Clinical studies of REVATIO did not include sufficient numbers of subjects aged 65 and over 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, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Patients with Hepatic Impairment No dose adjustment for mild to moderate impairment is required. Severe impairment has not been studied.

Patients with Renal Impairment No dose adjustment is required (including severe impairment CLcr <30 mL/min).

PATIENT COUNSELING INFORMATION

- Inform patients of contraindication of REVATIO with regular and/or intermittent use of organic nitrates.
- Inform patients that sildenafil is also marketed as VIAGRA for erectile dysfunction. Advise patients taking REVATIO not to take VIAGRA or other PDE-5 inhibitors.
- Advise patients to seek immediate medical attention for a sudden loss of vision in one or both eyes while taking REVATIO. Such an event may be a sign of NAION.
- Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking REVATIO. These events may be accompanied by tinnitus and dizziness.

Rx only Rev. June 2015

Few non-ICU patients receive palliative care consults

BY DOUG BRUNK
Frontline Medical News

AT CHEST 2016

LOS ANGELES – A significant percentage of patients who meet criteria for palliative care consultations do not receive a consult during their hospital stay, results from a single-center retrospective analysis showed.

"Physicians need to recognize the palliative care needs of patients with chronic illnesses other than malignancy before they get admitted to the ICU, especially when these patients are admitted repeatedly for the same problem [and] have a significant decline in functional status with a large symptom burden," Mohleen Kang, MD, said in an interview in advance of the annual meeting of the American College of Chest Physicians. "There is a potential missed opportunity for these conversations to occur with the patients and their family prior to their decompensation and crisis."

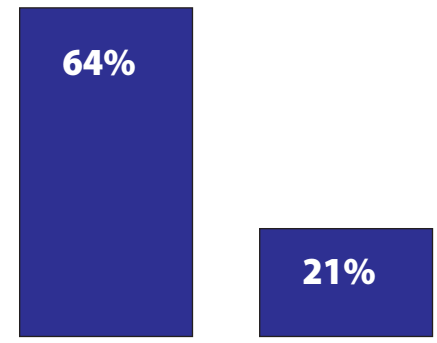
Twenty-nine percent (132) of the patients studied met an indication for a palliative care consult (PCC), with only 35 (27%) of such patients having received one. Patients with metastatic cancer were significantly more likely to have received a PCC, compared with noncancer patients (64% vs. 21%, respectively; *P* less than .001), while patients with New York Heart Association Class III or IV heart failure were less likely to receive a PCC, compared with those who did not have heart failure (5.6% vs. 29.8%; *P* = .014).

Criteria for PCC on admission include a life-limiting diagnosis and more than one admission in the past 3 months, decline in function, or complex care requirements. Criteria for PCC during hospitalization include life-limiting diagnosis and uncertainty about decisions, an ICU stay greater than 7 days, or lack of goals of care.

Dr. Kang, chief resident in the department of medicine at New Jersey Medical School, Newark, presented the results, which were of patients admitted to the department of medicine at University Hospital in Newark in 2015. Those admitted to the ICU within 24 hours of admission were excluded from the analysis, leaving 461 patient charts that were screened for PCC needs based on the consensus report from the Center to Advance Palliative Care.

The patients who met an indication for PCC had a mean age of 60 years and an average length of stay of 7 days. The percentages of these patients who were female, African American, and Hispanic were 45%, 40%, and 21%, respectively.

Patients with metastatic cancer were significantly more likely to have received a PCC, compared with noncancer patients



On multivariate analysis, patients who had a PCC within 72 hours of admission were 8 times more likely to have a hospital length of stay less than 7 days (*P* = .019), while those who had a PCC within 48 hours of admission were 20 times more likely to have a hospital length of stay less than 7 days (*P* = .017). "So if we intervened early, we were able to decrease their length of stay to less than 7 days," Dr. Kang said at the meeting.

She acknowledged certain limitations of the study, including its small sample size, retrospective design, and lack of follow-up. "This study also has a lot of confounding socioeconomic factors that do not make it applicable to every hospital across the country," she said. "This is not a homogeneous patient population."

The study's principal investigator was Anne Sutherland, MD, who is the medical intensive care unit director at University Hospital. Dr. Kang reported having no financial disclosures.

dbrunk@frontlinemedcom.com

Higher plasma sRAGE found in nonfocal ARDS

BY JIM KLING
Frontline Medical News

FROM CHEST

A biomarker may show whether acute respiratory distress syndrome (ARDS) is focal or nonfocal, a study showed.

This is an important distinction because some research suggests nonfocal ARDS, characterized by diffuse lung aeration loss, may have a worse prognosis and the two subtypes may respond differently to interventions such as positive end-expiratory pressure and recruitment maneuvers.

At present, the only way to identify focal versus nonfocal ARDS is a computed tomography scan, but that is often impractical because of the risks of moving the patient.

The current research, published in the November issue of CHEST (2016;150:998-1007), revealed that patients with nonfocal ARDS have higher plasma levels of the soluble form of the receptor for advanced glycation end product (sRAGE). At a cutoff of 1,188 pg/mL, the blood test differentiated between focal and nonfocal ARDS with a 94% sensitivity and an 84% specificity.

MARY JO DALES/FRONTLINE MEDICAL NEWS

We might conceive of using sRAGE as a marker for nonfocal ARDS, Dr. Ouellette said.

"Elevated baseline plasma sRAGE is a strong marker of nonfocal CT-based lung-imaging pattern in patients with early ARDS," reported Jean-Michel Constantin of University Hospital of Clermont-Ferrand (France) and colleagues in the Azurea network.

The researchers recruited 119 consecutive ARDS patients from 10 intensive care units in France. They measured plasma levels of sRAGE, plasminogen activator inhibitor–1 (PAI-1), soluble intercellular adhesion molecule–1, and surfactant protein–D within 24 hours of ARDS onset. Each patient underwent a lung CT scan within 48 hours to assess focal versus nonfocal lung morphology.

Twenty-seven percent of patients had focal ARDS, while 73% were categorized as nonfocal. Mean plasma levels of sRAGE were much higher in nonfocal patients (3,074 pg/mL vs. 877 pg/mL; *P* less than .001). A cutoff value of 1,188 ng/mL distinguished focal and nonfocal ARDS with a sensitivity of 93% (95% confidence interval, 85%-97%) and a specificity of 84% (95% CI, 66%-95%). The test's positive predictive value was 94% (95% CI, 87%-98%), and its negative predictive value was 81% (95% CI, 64%-93%).

The research is still in its early stage, but has a couple possible applications, according to Daniel R. Ouellette, MD, of Henry Ford Hospital, Detroit. "We might conceive of using this as a marker for nonfocal ARDS, and potentially use it to identify patients with worse outcomes. The other thing is, it may be a clue to help us learn about the underlying physiology of the disease," he said in an interview.

If physicians can confidently categorize a patient, it could inform treatment. "We know that patients who have diffuse disease may be more likely to be treated successfully with advanced ventilator techniques. These techniques would be more useful and likely to lead to recovery in patients that don't have focal disease," said Dr. Ouellette. "These results are exciting, but they are very preliminary."

The study was funded by the Auvergne Regional Council, the French Agence Nationale de la Recherche, and the Direction Generale de l'Offre de Soins, and the University Hospital of Clermont-Ferrand. The authors reported receiving funds from various pharmaceutical companies.

VIEW ON THE NEWS

sRAGE hints at mortality cause

"Mechanical stress is concentrated at the border zones between well-[aerated] and poorly aerated lung units, which is thought to predispose to mechanical lung injury in these regions during tidal ventilation. … The results of the current study support this possibility that mechanical lung injury persists in regions of stress concentration during low tidal volume ventilation, contributing to higher mortality in nonfocal ARDS.

"The current study also provides additional evidence that a plasma biomarker, such as sRAGE, could improve our ability to endotype patients with [acute respiratory distress syndrome], forecast prognosis, and identify subgroups for targeting of specific therapies early in the course of [acute respiratory distress syndrome]."

Michael A. Matthay, MD, is a professor of medicine and anesthesia at the University of California, San Francisco, and is with the Cardiovascular Research Institute. Dr. Matthay consults for Cerus Therapeutics, GlaxoSmithKline, Boerhinger-Ingleheim, Bayer, Biogen, Quark Pharmaceuticals, and Incardia. Jeremy R. Beitler, MD, is with the department of medicine at the University of California, San Diego. Dr. Beitler has received research support from Amgen and GlaxoSmithKline.

Sepsis survival rates highest in Northeast, metro areas

BY DOUG BRUNK
Frontline Medical News

AT CHEST 2016

LOS ANGELES – Compared with other parts of the United States, survival rates for sepsis were highest in the Northeast and in metropolitan areas in the Western regions of the United States, which mirrors the concentration of critical care fellowship programs, results from a descriptive analysis found.

"There must be consideration to redistribute the critical care work force based on the spread of the malady that they are trained to deal with," lead study author Aditya Shah, MD, said in an interview in advance of the annual meeting of the American College of Chest Physicians. "This could be linked to better reimbursements in the underserved areas."

Dr. Shah, an internal medicine resident at Advocate Christ Medical Center in Oak Lawn, Ill., and his associates, extracted sepsis mortality data from the National Center for Health Statistics (NCHS) Compressed Mortality File, which aggregates U.S. death incidence with regards to geographical distribution. They defined sepsis death as death attributed to an infection. The researchers used National Residency Matching Program data to determine the locations of current critical care fellowships. Next, they used Google fusion tables to map the data and studied them in relation to deaths attributed to infection in the continental United States, after running algorithms through the NCHS software, selecting deaths from infections, in age groups 20 years and older, in all races, and both sexes, with statewise charting of the data.

Dr. Aditya Shah called for consideration to redistribute critical care doctors.

Dr. Shah has conducted similar projects in patient populations with HIV and hepatitis, but to his knowledge, this is the first such analysis using NCHS data. "What is unique about this is that we can make real-time presentations to see how the work force and the pathology is evolving with regards to an epidemiological standpoint with real-time data, which can be easily accessed," he explained. "Depending on what we see, interventions and redistributions could be made with regards to better distributing providers based on where they are needed the most."

Of 150 critical care fellowship programs identified in the analysis, the majority were concentrated in the Northeast and metropolitan areas in the Western regions of the United States, which parallel similar patterns noted in other specialties. Survival rates for sepsis were also higher in these locations. Dr. Shah said that the findings support previous studies, which indicated that physicians often tend to practice in geographic areas close to their training sites. However, the fact that such variation existed in mortality from sepsis – one of the most-common diagnoses in the medical and surgical intensive care units – surprised him. "You would have thought that there would be a work force to deal with this malady," he said.

He acknowledged certain limitations of the study, including the fact that the NCHS data do not enable researchers to break down mortality from particular causes of sepsis. "Also, the most current data will always lag behind as it is entered retrospectively and needs time to be uploaded online," he said. "I am still in search of a more real-time database. However, that would require much more intensive time, money, and resources."

Dr. Shah reported having no financial disclosures.

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Dialysis need decreased with fluid administration in sepsis

BY M. ALEXANDER OTTO
Frontline Medical News

AT CHEST 2016

LOS ANGELES – Fluid administration of at least 1 L did not increase the incidence of acute respiratory or heart failure in severe sepsis, and actually seemed to decrease the need for dialysis in a review of 164 patients at Scott and White Memorial Hospital in Temple, Tex.

For every 1 mL of fluid administered per kg of body weight, the likelihood of dialysis decreased by 8.5% (odds ratio, 0.915; 95% confidence interval, 0.854-0.980; $P = .0111$), with no increase in heart or respiratory failure on univariate analysis. The 126 patients (77%) who received at least 1 L had a 68% reduction in the need for dialysis (OR, 0.32; CI, 0.117-0.890; $P = .0288$).

The findings come from a quality improvement project at the hospital launched after researchers there realized that the benchmark Surviving Sepsis Campaign guidelines weren't being met. The patients in the study had systolic blood pressures below 90 mm Hg or lactate levels of at least 4 mmol/L. The guidelines would have called for these patients to receive 30 mL/kg of crystalloid within 3 hours of presentation, but just 28 patients (17%) met that mark.

"The No. 1 reason we weren't meeting benchmarks was fluid administration," explained lead investigator Aruna Jahoor, MD, a pulmonary critical care and sleep medicine fellow at Texas Tech University Health Sciences Center, Lubbock.

Seventeen percent of patients received greater than or equal to 30 mL/kg of fluid resuscitation, while 28% received greater than or equal to 20 mL/kg of intravenous fluid resuscitation. It turned out that staff in the emergency department – where most of the patients were treated in the critical first 6 hours – were concerned about fluid overload and throwing patients into respiratory, heart, or renal failure, Dr. Jahoor said at the annual meeting of the American College of Chest Physicians. The team didn't find a difference in mortality when patients received 30 mL/kg – just over 2 L in a 70-kg patient – vs. 20 mL/kg or 1 L. The patients' in-hospital mortality rates and 28-day mortality rates were 27%, and 32%, respectively.

M. Alexander Otto/Frontline Medical News

"The No. 1 reason we weren't meeting benchmarks was fluid administration," Dr. Aruna Jahoor said.

There also weren't increased rates of heart failure, acute respiratory failure, or mechanical ventilation when patients received at least 1 L of fluid. "There were [also] lower rates of dialysis, which indicated that we weren't overloading patients. Even when we looked at fluid as a continuous variable, we still didn't see" complications, Dr. Jahoor said.

The findings should be reassuring to treating physicians. "When you have pushback against 30-mL/kg administration, you can say 'well, at least let's give a liter. You don't have to worry as much about some of the complications you are citing,'" she said.

For very obese patients, "it can get a little uncomfortable to be given" enough fluid to meet the 30-mL/kg goal, "but you can give at least a liter" without having to worry too much, she said. The patients in the study were treated from 2010 to 2013; normal saline was the most common resuscitation fluid. The hospital has since added the 30-mL/kg fluid resuscitation to its sepsis admission orders, and compliance has increased significantly.

A multivariate analysis is in the works to control for confounders. "We will probably [still] see you are not having increased rates of congestive heart or respiratory failure, or needing dialysis," Dr. Jahoor said. The protective effect against dialysis might drop out, "but I am hoping it doesn't," he said.

The investigators had no relevant financial disclosures.

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Combine qSOFA and SIRS for best sepsis score

BY M. ALEXANDER OTTO
Frontline Medical News

AT CHEST 2016

LOS ANGELES – Instead of replacing the Systemic Inflammatory Response Syndrome (SIRS) score with the new quick Sequential Organ Failure Assessment (qSOFA) score to identify severe sepsis patients, it might be best to use both, according to two studies presented at the American College of Chest Physicians annual meeting.

The gold standard 3rd International Consensus Definitions for Sepsis and Septic Shock Task Force recently introduced qSOFA to replace SIRS, in part because SIRS is too sensitive. With criteria that include a temperature above 38° C; a heart rate above 90 bpm, and a respiratory rate above 20 breaths per minute, it's possible to score positive on SIRS by walking up a flight of stairs, audience members at the study presentations noted.

The first study at the meeting session – a prospective cohort of 152 patients scored by both systems within 8 hours of ICU admission at the New York–Presbyterian Hospital – found that qSOFA was slightly better at predicting in-hospital mortality and ICU-free days, but no better than SIRS at predicting ventilator- or organ failure–free days.

However, of the 36% of patients (55) who met only one of the three qSOFA criteria – a respiratory rate of 22 breaths per minute, altered mental status, or a systolic blood pressure of 100 mg Hg or less – 6% (3) died in the hospital. Of those patients, two-thirds (2) were SIRS positive, meaning that they met two or more SIRS criteria.

"Having a borderline qSOFA of 1 point, which is considered negative, with the addition of having SIRS criteria, should raise concerns that patients need further evaluation. SIRS criteria should not be [entirely] discarded" in favor of qSOFA, said lead investigator Eli Finkelsztein, MD, of the New York–Presbyterian Hospital.

The second study – a review of 6,811 severe sepsis/septic shock patients scored by both systems within 3 hours of emergency department admission at the University of Kansas Hospital emergency department in Kansas City – found that the two scores performed largely the same when it came to predicting ICU admission and 30-day mortality, but that people who met two or more criteria in both systems were of special concern.

Twenty-five percent of patients (1,713) scored 2 or more on both SIRS and qSOFA. These patients were more likely to be admitted to the ICU and be readmitted to the hospital after a month, compared with those patients who were positive in only one scoring system or negative in both. Additional factors associated with these patients were that they had the longest ICU and hospital lengths of stay. Two hundred (12%) of these patients scoring 2 or more on both SIRS and qSOFA died within 30 days.

"SIRS criteria continue to be more sensitive at identifying severe sepsis, but they are equally as accurate [as qSOFA criteria] at predicting adverse patient outcomes," said lead investigator and Kansas University medical student Amanda Deis.

SIRS and qSOFA take only a few seconds to assess at the bedside. Using both builds "a clinical picture," she said.

There was no industry funding for the work, and the investigators had no relevant financial disclosures.

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VIEW ON THE NEWS

Screen with SIRS, admit with qSOFA

Everybody got fed up with SIRS because it's overly sensitive, but now we've swung in the other direction. It's absolutely true that qSOFA is more specific, but one of the presenters had a 6% rate of qSOFA missing sick patients.

We want to be somewhere in the middle in terms of not missing too many of these cases. I thought 6% was reasonable, but others may not.

Maybe a combination of the two is best. Using SIRS as ICU screening criteria might be a good idea; the ICU physician could then come in and use qSOFA to determine if someone needs to be admitted to the ICU.

Zaza Cohen, MD, is the director of critical care at Mountainside Hospital in Montclair, N.J. He moderated – but was not involved with – the two studies.

ECMO patients got relatively low sedative, analgesic doses

BY MARK S. LESNEY
Frontline Medical News

Patients on extracorporeal membrane oxygenation (ECMO) received relatively low doses of sedatives and analgesics while at a light level of sedation in a single-center prospective study of 32 patients.

In addition, patients rarely required neuromuscular blockade, investigators reported online in the Journal of Critical Care.

This finding contrasts with current guidelines on the management of pain, agitation, and delirium in patients on ECMO. The guidelines are based upon previous research that indicated the need for significant increases in sedative and analgesic doses, as well as the need for neuromuscular blockade, wrote Jeremy R. DeGrado, PharmD, of the department of pharmacy at Brigham and Women's Hospital, Boston, and his colleagues (J Crit Care. 2016 Aug 10;37:1-6. doi: 10.1016/j.jcrc.2016.07.020).

"Patients required significantly lower doses of opioids and sedatives than previously reported in the literature and did not demonstrate a need for increasing doses throughout the study period," the investigators said. "Continuous infusions of opioids were utilized on most ECMO days, but continuous infusions of benzodiazepines were used on less than half of all ECMO days."

Their 2-year, prospective, observational study assessed 32 adult intensive care unit patients on ECMO support for more than 48 hours. A total of 15 patients received VA (venoarterial) ECMO and 17 received VV (venovenous) ECMO. Patients received a median daily dose of benzodiazepines (midazolam equivalents) of 24 mg and a median daily dose of opioids (fentanyl equivalents) of 3,875 mcg.

"Continuous infusions of opioids were utilized on most ECMO days, but continuous infusions of benzodiazepines were used on less than half of all ECMO days."

The primary indication for VA ECMO was cardiogenic shock, while VV ECMO was mainly used as a bridge to lung transplant or in patients with severe acute respiratory distress syndrome. The researchers evaluated a total of 475 ECMO days: 110 VA ECMO and 365 VV ECMO.

On average, patients were sedated to Richmond Agitation Sedation Scale scores between 0 and −1. Across all 475 ECMO days, patients were treated with continuous infusions of opioids (on 85% of ECMO days), benzodiazepines (42%), propofol (20%), dexmedetomidine (7%), and neuromuscular blocking agents (13%).

In total, patients who received VV ECMO had a higher median dose of opioids and trended toward a lower dose of benzodiazepines than did those who received VA ECMO, Dr. DeGrado and his associates reported.

In total, patients in the VA arm, compared with those in the VV arm, more frequently received a continuous infusion opioid (96% vs. 82% of days) and a benzodiazepine (58% vs. 37% of days). These differences were statistically significant.

Adjunctive therapies, including antipsychotics and clonidine, were administered frequently, according to the report.

"We did not observe an increase in dose requirement over time during ECMO support, possibly due to a multimodal pharmacologic approach. Overall, patients were not deeply sedated and rarely required neuromuscular blockade. The hypothesis that patients on ECMO require high doses of sedatives and analgesics should be further investigated," the researchers concluded.

The authors reported that they had no disclosures.

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Reach with Confidence for **24-hour BREO**

For adult patients with asthma uncontrolled on an ICS or whose disease severity clearly warrants an ICS/LABA. BREO is NOT indicated for the relief of acute bronchospasm.

Important Safety Information

WARNING: ASTHMA-RELATED DEATH

- **Long-acting beta$_2$-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths. This finding with salmeterol is considered a class effect of all LABA. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids (ICS) or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients.**
- **When treating patients with asthma, only prescribe BREO for patients not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue BREO) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS. Do not use BREO for patients whose asthma is adequately controlled on low- or medium-dose ICS.**

CONTRAINDICATIONS

- BREO is contraindicated for primary treatment of status asthmaticus or other acute episodes of chronic obstructive pulmonary disease (COPD) or asthma where intensive measures are required.
- BREO is contraindicated in patients with severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone furoate, vilanterol, or any of the excipients.

Please see additional Important Safety Information on the following pages.
Please see Brief Summary of Prescribing Information, including Boxed Warning, for BREO on the pages following this advertisement.

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BREO offers patients proven efficacy with just one daily dose

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

Deliver 24-hour lung function improvement

with one inhalation, once daily*

Reduce asthma exacerbations

in patients with a history of exacerbations†

Supporting Clinical Study Information

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

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

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

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS

- BREO should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD or asthma.
- BREO should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled, short-acting $beta_2$-agonist.
- BREO should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using BREO should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
- Oropharyngeal candidiasis has occurred in patients treated with BREO. Advise patients to rinse the mouth with water without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.
- Patients who use corticosteroids are at risk for potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. A more serious or even fatal course of chickenpox or measles may occur in susceptible patients. Use caution in patients with the above because of the potential for worsening of these infections.
- Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. Taper patients slowly from systemic corticosteroids if transferring to BREO.

WARNINGS AND PRECAUTIONS (cont'd)

- 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 immediately and institute alternative therapy.
- Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of BREO. Discontinue BREO if such reactions occur.
- Vilanterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, BREO may need to be discontinued. BREO should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
- Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care.

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The information provided is not a guarantee of coverage or payment (partial or full). Please verify coverage with and obtain most current information from plan sponsors. GSK does not endorse individual plans.

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD or asthma following the long-term administration of inhaled corticosteroids. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Be alert to hypokalemia and hyperglycemia.
- Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to children and adolescents.

ADVERSE REACTIONS

- In a 12-week trial, adverse reactions (≥2% incidence and more common than placebo) reported in subjects taking BREO 100/25 (and placebo) were: nasopharyngitis, 10% (7%); headache, 5% (4%); oropharyngeal pain, 2% (1%); oral candidiasis, 2% (0%); and dysphonia, 2% (0%). In a separate 12-week trial, adverse reactions (≥2% incidence) reported in subjects taking BREO 200/25 (or BREO 100/25) were: headache, 8% (8%); nasopharyngitis, 7% (6%); influenza, 3% (3%); upper respiratory tract infection, 2% (2%); oropharyngeal pain, 2% (2%); sinusitis, 2% (1%); bronchitis, 2% (<1%); and cough, 1% (2%).
- In addition to the adverse reactions reported in the two 12-week trials, adverse reactions (≥2% incidence) reported in subjects taking BREO 200/25 once daily in a 24-week trial included viral respiratory tract infection, pharyngitis, pyrexia, and arthralgia, and with BREO 100/25 or 200/25 in a 12-month trial included pyrexia, back pain, extrasystoles, upper abdominal pain, respiratory tract infection, allergic rhinitis, pharyngitis, rhinitis, arthralgia, supraventricular extrasystoles, ventricular extrasystoles, acute sinusitis, and pneumonia.

ADVERSE REACTIONS (cont'd)

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

References: 1. Bernstein DI et al. *J Asthma.* 2015;52(10):1073-1083. **2.** Bleecker ER et al. *J Allergy Clin Immunol Pract.* 2014;2(5):553-561. **3.** Bateman ED et al. *Thorax.* 2014;69(4):312-319.

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

BRIEF SUMMARY

BREO® ELLIPTA® 100/25 (fluticasone furoate 100 mcg and vilanterol 25 mcg inhalation powder), for oral inhalation
BREO® ELLIPTA® 200/25 (fluticasone furoate 200 mcg and vilanterol 25 mcg inhalation powder), for oral inhalation

The following is a brief summary only and is focused on the asthma indication. See full prescribing information for complete product information.

WARNING: ASTHMA-RELATED DEATH

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

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

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Asthma-Related Death LABA, such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of ICS or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, physicians should only prescribe BREO for patients not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue BREO) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS. Do not use BREO for patients whose asthma is adequately controlled on low- or medium-dose ICS. A 28-week, placebo-controlled, US trial that compared the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs. 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). The increased risk of asthma-related death is considered a class effect of LABA, including vilanterol, one of the active ingredients in BREO. No trial adequate to determine whether the rate of asthma-related death is increased in subjects treated with BREO has been conducted.
5.2 Deterioration of Disease and Acute Episodes BREO should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD or asthma. BREO has not been studied in subjects with acutely deteriorating COPD or asthma. The initiation of BREO in this setting is not appropriate. Increasing use of inhaled, short-acting beta$_2$-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of BREO with a higher strength, adding additional ICS, or initiating systemic corticosteroids. Patients should not use more than 1 inhalation once daily of BREO. BREO should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. BREO has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist. When beginning treatment with BREO, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms. When prescribing BREO, the healthcare provider should also prescribe an inhaled, short-acting beta$_2$-agonist and instruct the patient on how it should be used.
5.3 Excessive Use of BREO and Use with Other Long-Acting Beta$_2$-Agonists BREO should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using BREO should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
5.4 Local Effects of ICS In clinical trials, the development of localized infections of the mouth and pharynx with *Candida albicans* has occurred in subjects treated with BREO. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while treatment with BREO continues, but at times therapy with BREO may need to be interrupted. Advise the patient to rinse his/her mouth with water without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.
5.6 Immunosuppression Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If a patient is exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered. ICS should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.
5.7 Transferring Patients from Systemic Corticosteroid Therapy Particular care is needed for patients who have been transferred from systemically active corticosteroids to ICS because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available ICS. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. Patients who have been previously maintained on 20 mg or more of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although BREO may control COPD or asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies. During periods of stress, a severe COPD exacerbation, or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress, a severe COPD exacerbation, or a severe asthma attack. Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to BREO. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with BREO. Lung function (FEV_1 or peak expiratory flow), beta-agonist use, and COPD or asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension. Transfer of patients from systemic corticosteroid therapy to BREO may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions). During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.
5.8 Hypercorticism and Adrenal Suppression Inhaled fluticasone furoate is absorbed into the circulation and can be systemically active. Effects of fluticasone furoate on the HPA axis are not observed with the therapeutic doses of BREO. However, exceeding the recommended dosage or coadministration with a strong cytochrome P450 3A4 (CYP3A4) inhibitor may result in HPA dysfunction *[see Warnings and Precautions (5.9), Drug Interactions (7.1)]*. Because of the possibility of significant systemic absorption of ICS in sensitive patients, patients treated with BREO should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response. It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients who are sensitive to these effects. If such effects occur, BREO should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids, and other treatments for management of COPD or asthma symptoms should be considered.
5.9 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors Caution should be exercised when considering the coadministration of BREO with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full prescribing information]*.
5.10 Paradoxical Bronchospasm As with other inhaled medicines, BREO can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with BREO, it should be treated immediately with an inhaled, short-acting bronchodilator; BREO should be discontinued immediately; and alternative therapy should be instituted.
5.11 Hypersensitivity Reactions, Including Anaphylaxis Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of BREO. Discontinue BREO if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder medications containing lactose; therefore, patients with severe milk protein allergy should not use BREO *[see Contraindications (4)]*.
5.12 Cardiovascular Effects Vilanterol, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, BREO may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. In healthy subjects, large doses of inhaled fluticasone furoate/vilanterol (4 times the recommended dose of vilanterol, representing a 12- or 10-fold higher systemic exposure than seen in subjects with COPD or asthma, respectively) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias. Therefore, BREO, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
5.13 Reduction in Bone Mineral Density Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing ICS. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care.
5.14 Glaucoma and Cataracts Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD or asthma following the long-term administration of ICS. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.
5.15 Coexisting Conditions BREO, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.
5.16 Hypokalemia and Hyperglycemia Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medications may produce transient hyperglycemia in some patients. In clinical trials evaluating BREO in subjects with COPD or asthma, there was no evidence of a treatment effect on serum glucose or potassium.
5.17 Effect on Growth Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to children and adolescents. *[See Use in Specific Populations (8.4) of full prescribing information.]*

6 ADVERSE REACTIONS

LABA, such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of ICS or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. *[See Warnings and Precautions (5.1).]* Systemic and local corticosteroid use may result in the following: *Candida albicans* infection *[see Warnings and Precautions (5.4)]*; Immunosuppression *[see Warnings and Precautions (5.6)]*; Hypercorticism and adrenal suppression *[see Warnings and Precautions (5.8)]*; Reduction in bone mineral density *[see Warnings and Precautions (5.13)]*. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.
6.2 Clinical Trials Experience in Asthma BREO for the treatment of asthma was studied in 18 double-blind, parallel-group, controlled trials (11 with placebo) of 4 to 76 weeks' duration, which enrolled 9,969 subjects with asthma. BREO 100/25 was studied in 2,369 subjects and BREO 200/25 was studied in 956 subjects. While subjects aged 12 to 17 years were included in these trials, BREO is not approved for use in this age-group *[see Use in Specific Populations (8.4)]*. The safety data described below are based on two 12-week efficacy trials, one 24-week efficacy trial, and two long-term trials.
12-Week Trials Trial 1 was a 12-week trial that evaluated the efficacy of BREO 100/25 in adolescent and adult subjects with asthma compared with fluticasone furoate 100 mcg and placebo. Of the 609 subjects, 58% were female and 84% were white; the mean age was 40 years.
In Trial 1, adverse reactions (≥2% incidence and more common than placebo) reported in subjects with asthma taking BREO 100/25 (n=201) (fluticasone furoate 100 mcg [n=205] or placebo [n=203]) were: nasopharyngitis,

10% (7%, 7%); headache, 5% (4%, 4%); oropharyngeal pain, 2% (2%, 1%); oral candidiasis, 2% (2%, 0%); and dysphonia, 2% (1%, 0%). Oral candidiasis includes oral candidiasis and oropharyngeal candidiasis.
Trial 2 was a 12-week trial that evaluated the efficacy of BREO 100/25, BREO 200/25, and fluticasone furoate 100 mcg in adolescent and adult subjects with asthma. This trial did not have a placebo arm. Of the 1,039 subjects, 60% were female and 88% were white; the mean age was 46 years.
In Trial 2, adverse reactions (≥2% incidence) reported in subjects with asthma taking BREO 200/25 (n=346) (BREO 100/25 [n=346] or fluticasone furoate 100 mcg [n=347]) were: headache, 8% (8%, 9%); nasopharyngitis, 7% (6%, 7%); influenza, 3% (3%, 1%); upper respiratory tract infection, 2% (2%, 3%); oropharyngeal pain, 2% (2%, 1%); sinusitis, 2% (1%, <1%); bronchitis, 2% (<1%, 2%); and cough, 1% (2%, 1%).
24-Week Trial Trial 3 was a 24-week trial that evaluated the efficacy of BREO 200/25 once daily, fluticasone furoate 200 mcg once daily, and fluticasone propionate 500 mcg twice daily in adolescent and adult subjects with asthma. Of the 586 subjects, 59% were female and 84% were white; the mean age was 46 years. This trial did not have a placebo arm. In addition to the reactions shown for Trials 1 and 2 above, adverse reactions occurring in greater than or equal to 2% of subjects treated with BREO 200/25 included viral respiratory tract infection, pharyngitis, pyrexia, and arthralgia.
12-Month Trial Long-term safety data is based on a 12-month trial that evaluated the safety of BREO 100/25 once daily (n = 201), BREO 200/25 once daily (n = 202), and fluticasone propionate 500 mcg twice daily (n = 100) in adolescent and adult subjects with asthma (Trial 4). Overall, 63% were female and 67% were white. The mean age was 39 years; adolescents (aged 12 to 17 years) made up 16% of the population. In addition to the reactions shown for Trials 1 and 2 above, adverse reactions occurring in greater than or equal to 2% of the subjects treated with BREO 100/25 or BREO 200/25 for 12 months included pyrexia, back pain, extrasystoles, upper abdominal pain, respiratory tract infection, allergic rhinitis, pharyngitis, rhinitis, arthralgia, supraventricular extrasystoles, ventricular extrasystoles, acute sinusitis, and pneumonia.
Exacerbation Trial In a 24- to 76-week trial, subjects received BREO 100/25 (n = 1,009) or fluticasone furoate 100 mcg (n = 1,010) (Trial 5). Subjects participating in this trial had a history of one or more asthma exacerbations that required treatment with oral/systemic corticosteroids or emergency department visit or in-patient hospitalization for the treatment of asthma in the year prior to trial entry. Overall, 67% were female and 73% were white; the mean age was 42 years (adolescents aged 12 to 17 years made up 14% of the population). While subjects aged 12 to 17 years were included in this trial, BREO is not approved for use in this age-group *[see Use in Specific Populations (8.4)]*. Asthma-related hospitalizations occurred in 10 subjects (1%) treated with BREO 100/25 compared with 7 subjects (0.7%) treated with fluticasone furoate 100 mcg. Among subjects aged 12 to 17 years, asthma-related hospitalizations occurred in 4 subjects (2.6%) treated with BREO 100/25 (n = 151) compared with 0 subjects treated with fluticasone furoate 100 mcg (n = 130). There were no asthma-related deaths or asthma-related intubations observed in this trial.

6.3 Postmarketing Experience In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of BREO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to BREO or a combination of these factors.
Cardiac Disorders Palpitations, tachycardia.
Immune System Disorders Hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria.
Musculoskeletal and Connective Tissue Disorders Muscle spasms.
Nervous System Disorders Tremor.
Psychiatric Disorders Nervousness.
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 for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.
7.4 Non–Potassium-Sparing Diuretics The electrocardiographic changes and/or hypokalemia that may result from the administration of non–potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with non–potassium-sparing diuretics.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Teratogenic Effects Pregnancy Category C. There are no adequate and well-controlled trials with BREO in pregnant women. Corticosteroids and beta$_2$-agonists have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Because animal reproduction studies are not always predictive of human response, BREO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women should be advised to contact their physicians if they become pregnant while taking BREO. *Fluticasone Furoate and Vilanterol:* There was no evidence of teratogenic interactions between fluticasone furoate and vilanterol in rats at approximately 5 and 40 times, respectively, the maximum recommended human daily inhalation dose (MRHDID) in adults (on a mcg/m^2 basis at maternal inhaled doses of fluticasone furoate and vilanterol, alone or in combination, up to approximately 95 mcg/kg/day). *Fluticasone Furoate:* There were no teratogenic effects in rats and rabbits at approximately 4 and 1 times, respectively, the MRHDID in adults (on a mcg/m^2 basis at maternal inhaled doses up to 91 and 8 mcg/kg/day in rats and rabbits, respectively). There were no effects on perinatal and postnatal development in rats at approximately 1 time the MRHDID in adults (on a mcg/m^2 basis at maternal doses up to 27 mcg/kg/day). *Vilanterol:* There were no teratogenic effects in rats and rabbits at approximately 13,000 and 160 times, respectively, the MRHDID in adults (on a mcg/m^2 basis at maternal inhaled doses up to 33,700 mcg/kg/day in rats and on an AUC basis at maternal inhaled doses up to 591 mcg/kg/day in rabbits). However, fetal skeletal variations were observed in rabbits at approximately 1,000 times the MRHDID in adults (on an AUC basis at maternal inhaled or subcutaneous doses of 5,740 or 300 mcg/kg/day, respectively). The skeletal variations included decreased or absent ossification in cervical vertebral centrum and metacarpals. There were no effects on perinatal and postnatal development in rats at approximately 3,900 times the MRHDID in adults (on a mcg/m^2 basis at maternal oral doses up to 10,000 mcg/kg/day).
Nonteratogenic Effects Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully monitored.
8.2 Labor and Delivery There are no adequate and well-controlled human trials that have investigated the effects of BREO during labor and delivery. Because beta-agonists may potentially interfere with uterine contractility, BREO should be used during labor only if the potential benefit justifies the potential risk.
8.3 Nursing Mothers It is not known whether fluticasone furoate or vilanterol are excreted in human breast milk. However, other corticosteroids and beta$_2$-agonists have been detected in human milk. Since there are no data from controlled trials on the use of BREO by nursing mothers, caution should be exercised when it is administered to a nursing woman.
8.4 Pediatric Use BREO is not indicated for use in children and adolescents. The safety and efficacy in pediatric patients (aged 17 years and younger) have not been established. In a 24- to 76-week exacerbation trial, subjects received BREO 100/25 (n = 1,009) or fluticasone furoate 100 mcg (n = 1,010). Subjects had a mean age of 42 years and a history of one or more asthma exacerbations that required treatment with oral/systemic corticosteroids or emergency department visit or in-patient hospitalization for the treatment of asthma in the year prior to study entry. *[See Clinical Studies (14.2) of full prescribing information.]* Adolescents aged 12 to 17 years made up 14% of the study population (n = 281), with a mean exposure of 352 days for subjects in this age-group treated with BREO 100/25 (n = 151) and 355 days for subjects in this age-group treated with fluticasone furoate 100 mcg (n = 130). In this age-group, 10% of subjects treated with BREO 100/25 reported an asthma exacerbation compared with 7% for subjects treated with fluticasone furoate 100 mcg. Among the adolescents, asthma-related hospitalizations occurred in 4 subjects (2.6%) treated with BREO 100/25 compared with 0 subjects treated with fluticasone furoate 100 mcg. There were no asthma-related deaths or asthma-related intubations observed in the adolescent age-group.
Effects on Growth Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to children and adolescents. A reduction of growth velocity in children and adolescents may occur as a result of poorly controlled asthma or from use of corticosteroids, including ICS. The effects of long-term treatment of children and adolescents with ICS, including fluticasone furoate, on final adult height are not known. *[See Warnings and Precautions (5.17); Use in Special Populations (8.4) of full prescribing information.]*
8.5 Geriatric Use Based on available data, no adjustment of the dosage of BREO in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out. Clinical trials of BREO for asthma included 854 subjects aged 65 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects.
8.6 Hepatic Impairment Fluticasone furoate systemic exposure increased by up to 3-fold in subjects with hepatic impairment compared with healthy subjects. Hepatic impairment had no effect on vilanterol systemic exposure. Use BREO with caution in patients with moderate or severe hepatic impairment. Monitor patients for corticosteroid-related side effects *[see Clinical Pharmacology (12.3) of full prescribing information]*.
8.7 Renal Impairment There were no significant increases in either fluticasone furoate or vilanterol exposure in subjects with severe renal impairment (CrCl less than 30 mL/min) compared with healthy subjects. No dosage adjustment is required in patients with renal impairment *[see Clinical Pharmacology (12.3) of full prescribing information]*.

10 OVERDOSAGE

No human overdosage data has been reported for BREO. BREO contains both fluticasone furoate and vilanterol; therefore, the risks associated with overdosage for the individual components described below apply to BREO. Treatment of overdosage consists of discontinuation of BREO together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medicine can produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage.
10.1 Fluticasone Furoate Because of low systemic bioavailability (15.2%) and an absence of acute drug-related systemic findings in clinical trials, overdosage of fluticasone furoate is unlikely to require any treatment other than observation. If used at excessive doses for prolonged periods, systemic effects such as hypercorticism may occur *[see Warnings and Precautions (5.8)]*. Single- and repeat-dose trials of fluticasone furoate at doses of 50 to 4,000 mcg have been studied in human subjects. Decreases in mean serum cortisol were observed at dosages of 500 mcg or higher given once daily for 14 days.
10.2 Vilanterol The expected signs and symptoms with overdosage of vilanterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms of beta-adrenergic stimulation (e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, hyperglycemia, hypokalemia, metabolic acidosis). As with all inhaled sympathomimetic medicines, cardiac arrest and even death may be associated with an overdose of vilanterol.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).
Asthma-Related Death **Inform patients with asthma that LABA, such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death and may increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Also inform them that currently available data are inadequate to determine whether concurrent use of ICS or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA.**
Not for Acute Symptoms Inform patients that BREO is not meant to relieve acute symptoms of COPD or asthma and extra doses should not be used for that purpose. Advise patients to treat acute symptoms with an inhaled, short-acting beta$_2$-agonist such as albuterol. Provide patients with such medication and instruct them in how it should be used. Instruct patients to seek medical attention immediately if they experience any of the following: Decreasing effectiveness of inhaled, short-acting beta$_2$-agonists; Need for more inhalations than usual of inhaled, short-acting beta$_2$-agonists; Significant decrease in lung function as outlined by the physician. Tell patients they should not stop therapy with BREO without physician/provider guidance since symptoms may recur after discontinuation.
Do Not Use Additional Long-acting Beta$_2$-agonists Instruct patients not to use other LABA for COPD and asthma.
Local Effects Inform patients that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing therapy with BREO, but at times therapy with BREO may need to be temporarily interrupted under close medical supervision. Advise patients to rinse the mouth with water without swallowing after inhalation to help reduce the risk of thrush.
Immunosuppression Warn patients who are on immunosuppressant doses of corticosteroids to avoid exposure to chickenpox or measles and, if exposed, to consult their physicians without delay. Inform patients of potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.
Hypercorticism and Adrenal Suppression Advise patients that BREO may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, inform patients that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to BREO.
Reduction in Bone Mineral Density Advise patients who are at an increased risk for decreased BMD that the use of corticosteroids may pose an additional risk.
Ocular Effects Inform patients that long-term use of ICS may increase the risk of some eye problems (cataracts or glaucoma); consider regular eye examinations.
Risks Associated with Beta-agonist Therapy Inform patients of adverse effects associated with beta$_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.
Hypersensitivity Reactions, Including Anaphylaxis Advise patients that hypersensitivity reactions (e.g., anaphylaxis, angioedema, rash, urticaria) may occur after administration of BREO. Instruct patients to discontinue BREO if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder medications containing lactose; therefore, patients with severe milk protein allergy should not use BREO.

BREO was developed in collaboration with Theravance.

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Home oxygen upped survival in some PAH patients

BY KATIE WAGNER LENNON
Frontline Medical News

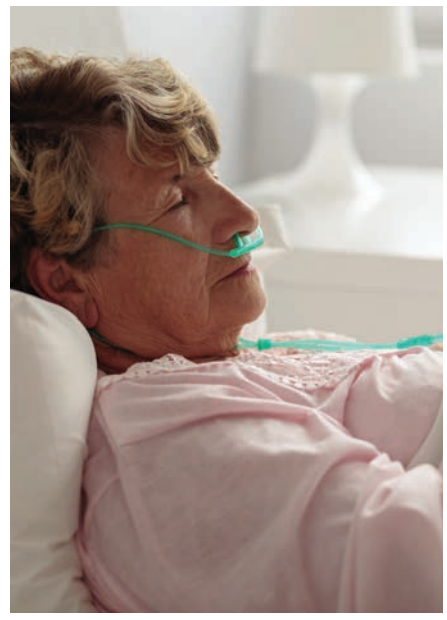
AT CHEST 2016

LOS ANGELES – Pulmonary arterial hypertension (PAH) patients with severely impaired diffusing capacity of the lungs for carbon monoxide (DLCO) were much more likely to survive when they received home oxygen therapy, according to a disease registry analysis.

"We all know that supplemental oxygen is widely used with PAH," said Harrison W. Farber, MD, director of the pulmonary hypertension center at Boston University. But there are practically no data showing that it is successful, and there are even fewer data for patients with PAH who have very low diffusion capacity, he added.

That knowledge gap prompted Dr. Farber and his colleagues to analyze data from REVEAL (the Registry to Evaluate Early and Long-Term PAH Disease Management), the largest disease registry in the world of patients with PAH.

"Patients in that group – the severe DLCO group – who got oxygen had poorer prognostic features but improved overall survival relative to those who didn't," Dr. Farber explained during a presentation at the annual meeting of the American College of Chest Physicians. "Based on this, it makes us think that home oxygen, supplemental oxygen treatment, is associated with improved survival in patients, especially those with severe DLCO and PAH."



KATARZYNABIALASIEWICZ/THINKSTOCK

The 3,046 patients analyzed by Dr. Farber and his colleagues had World Health Organization Group 1 PAH with right heart catheterization hemodynamic criteria: a mean pulmonary artery pressure greater than 25 mm Hg, a pulmonary capillary wedge pressure less than or equal to 15 mm Hg, and a pulmonary vascular resistance of at least 3 Wood units (WU). Patients were at least 18 years of age and grouped by oxygen use, which was defined as any use at any time from study enrollment to the end of follow-up, and by DLCO group.

A total of 57% of the patients (1,734) received oxygen, and the remaining 43% of the patients (1,312) did not receive oxygen. Among the patients who received oxygen, 71% (1,227) received the therapy continuously, and 24% (408) received oxygen at night only.

The 424 patients with a DLCO of less than 40% were considered to have a severe DLCO impairment. The other two groups comprised 505 patients with a moderate DLCO impairment (at least 40%, but less than 60%) and 844 patients with a mild to normal DLCO (at least 60%). The DLCOs of 1,273 patients analyzed were unknown.

Among those patients with severe DLCO impairment, the risk of death was significantly lower in those who received oxygen, compared with those who did not receive oxygen (hazard ratio, 0.56; $P = .0033$). Oxygen use was associated with significant improvements in overall survival in both the newly diagnosed (HR, 0.47; $P = .029$) and previously diagnosed (HR, 0.59; $P = .026$) severe DLCO cohorts, Dr. Farber said.

Patients receiving oxygen were more likely to be treated with PAH-specific medications, regardless of their DLCO group.

Among the analysis's limitations was that the lengths of time patients had been undergoing oxygen treatment were unknown. That prevented adjustments for duration of oxygen treatment, according to Dr. Farber.

Dr. Farber disclosed serving on the steering committees or advisory boards for Actelion, Bayer, Bellerophon, Gilead, and United Therapeutics. He has received research support from Actelion, Gilead, and United Therapeutics, and has been a speaker for Actelion, Bayer, and Gilead.

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Riociguat helps poor responders to PDE inhibitors

BY M. ALEXANDER OTTO
Frontline Medical News

AT CHEST 2016

LOS ANGELES – Pulmonary artery hypertension patients who have an insufficient response to phosphodiesterase (PDE) inhibitors may benefit from a switch to riociguat (Adempas), based on results from a 24-week, open-label investigation from the drug's maker, Bayer.

The 61 patients – mean age 54 years, 74% of whom were women – had World Health Organization functional class 3 disease, with 6-minute walking distances of 165-440 meters, and cardiac indices below 3 L per min/m^2 despite being on a PDE inhibitor for 90 days or more, 40 (66%) on sildenafil (Viagra) and 21 (34%) on tadalafil (Cialis).

After PDE inhibitor washout, the researchers swapped them for riociguat titrated to a maximum oral dose of 2.5 mg t.i.d. The 50 patients (82%) on concomitant endothelin receptor antagonists (ERA) were allowed to stay on them. At week 24, 16 patients (34% of the 47 evaluable patients) achieved the combined endpoint of no clinical worsening, functional class 1 or 2, and 30 meters or more improvement on their walk test.

Two of 10 serious adverse events were deemed to be drug related. The label for riociguat – already on the U.S. market for pulmonary artery hypertension (PAH) – warns of symptomatic hypotension, bleeding, and pulmonary edema in patients with pulmonary veno-occlusive disease.

"The key point is that it was safe to switch people from a [PDE inhibitor] to riociguat, and it seemed to have improved efficacy, but we hesitate on these conclusions because it was an open-label trial, and the results need to be confirmed," lead investigator James Klinger, FCCP, MD, professor of medicine at Brown University, Providence, R.I., said at the annual meeting of the American College of Chest Physicians. A randomized, controlled trial is underway, he added.

Switching people from a phosphodiesterase inhibitor to riociguat was safe and possibly more efficacious.

DR. KLINGER

The usual approach to PAH is to start patients on a PDE inhibitor, often with an ERA. If that doesn't work, a prostacyclin is added. The cost can exceed $200,000 a year.

"This is a study that says, wait a minute, before you add a third drug to the first two, maybe it would be worthwhile to" switch out the PDE inhibitor. "You would save the person the addition of a third drug," and the cost would be comparable or less than a three-drug regimen, Dr. Klinger said.

The researchers also found that after 24 weeks on riociguat, mean plasma cyclic guanosine monophosphate (cGMP) increased by 4.6 pmol/mL, urinary cGMP by 1,005 pmol/mL, and asymmetric dimethylarginine (ADMA) by 0.004 micromol/L.

The biomarkers were important because the team is trying to find a way to identify patients who would benefit most from riociguat. "As a field, we still don't understand the disease well enough to know" how to best match patients and drugs. "We are trying to find a biomarker that would identify patients who are more likely to respond to one medication versus another," Dr. Klinger said.

ADMA inhibits the production of nitric oxide, and is a bad player in PAH. The study results were reassuring because riociguat didn't have much of an effect on ADMA levels, although the "slight difference was not enough to identify people who might do better with" it, Dr. Klinger said.

As for cGMP, "when we raise [levels] with riociguat, patients get better, so we think riociguat is raising cGMP in the right place, which we think is the lungs. Unfortunately, we don't' have a biomarker that can distinguish lung cGMP from total body cGMP," he said.

The work was funded by Bayer, maker of riociguat. Dr. Klinger is an unpaid consultant, and also receives research support from the company.

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Consider mitral valve repair in PH with dyspnea

BY M. ALEXANDER OTTO
Frontline Medical News

EXPERT ANALYSIS FROM CHEST 2016

LOS ANGELES – Dyspnea in pulmonary hypertension (PH) is caused by mitral valve disease until proven otherwise, according to Paul Forfia, MD, director of pulmonary hypertension, right heart failure, and pulmonary thromboendarterectomy at Temple University, Philadelphia.

Although mitral valve disease is a well-recognized cause of PH, its significance is often underestimated in practice.

"Whether the valve is regurgitant or stenotic makes absolutely no difference. When you delay" repair or replacement, "the patient keeps getting sicker," he said.

In time, "everyone is standing around wringing their hands going, 'Oh my god, what are we going to do?' Are you serious? Fix the valve. We see this type of patient a couple times a month," Dr. Forfia said at the American College of Chest Physicians annual meeting.

"I have seen lifesaving mitral valve surgery put off for many years in patients with pulmonary hypertension, when all they needed was to have their valve fixed," he said.

A few things could explain the problem. Prevention of rheumatic fever has made mitral stenosis far less common than in the past, so cardiologists may not be as good at diagnosing it. The increased attention on PH in recent years may also have eclipsed the importance of underlying mitral valve disease and the need to address it, said Dr. Forfia.

Whatever the case, pulmonologists who want the valve fixed often end up playing patient ping pong with cardiologists who want the hypertension controlled beforehand, but "if I treat the pulmonary circulation first, all I am going to do is unmask the left heart failure. There will be no functional improvement whatsoever," Dr. Forfia said.

Surgery is the best solution as long as patients are well enough to recover. "With pulmonary hypertension in the setting of severe mitral valve regurgitation or stenosis, whether the pulmonary hypertension is related to passive left heart congestion or associated with pulmonary arteriopathy, the only sensible option is to correct the underlying valvular abnormality,"

FRONTLINE MEDICAL NEWS©

Mitral valve surgery can be lifesaving, Dr. Paul Forfia said.

he said. The surgery should be done at an institution capable of managing postop pulmonary arteriopathy, if present.

An expert pulmonology center will spot the mitral valve problem right away.

"There is no pulmonary pressure cutoff that should prohibit surgery" in patients able to recover. "There is no such thing as a pulmonary artery pressure too high to be explained by mitral valve disease. The pulmonary pressure can be as high as it wants to be. You will get nowhere by thinking the pressure is too high to address the valve," Dr. Forfia said.

Often "you hear, 'I'm afraid the person is going to die on the table.' I always say 'If the patient is not going to die on the table, they are going to die in their living room of progressive heart failure because you [didn't] fix their valve. I have never had a patient with pulmonary hypertension not separate from cardiopulmonary bypass. It's a myth," he said.

When there's a "question if the dyspnea is coming from the mitral valve, we routinely use exercise right heart catheterization to probe the situation. We have a recumbent bike in the cath lab. You'll often provoke significant left heart congestion with a low workload. It's very revealing to the significance of mitral valve disease," he said. Aortic valve disease is also missed in pulmonary hypertension. "It's not [a] similar" problem; "it's the same" problem, Dr. Forfia said.

Dr. Forfia is a consultant for Bayer, Actelion, and United Therapeutics.

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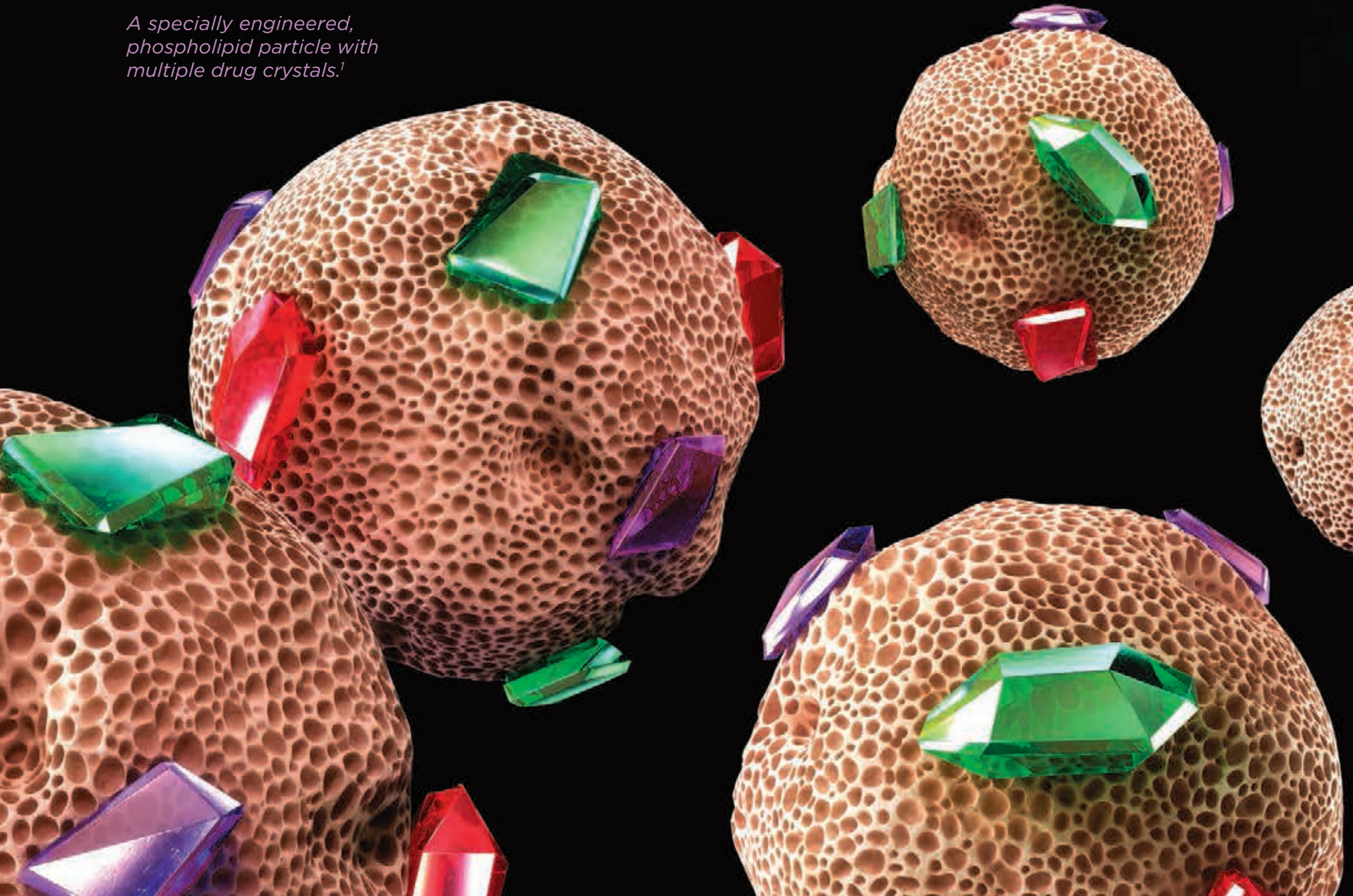

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All images are for illustrative purposes only.

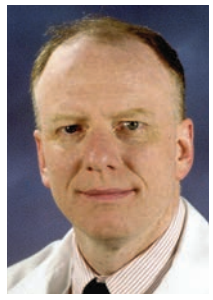
Reference: 1. Vehring R et al. *Langmuir*. 2012;28(42):15015-15023.

AstraZeneca

Update on NAMDRC activities

BY CHARLES W. ATWOOD JR., MD, FCCP
NAMDRC President-Elect

The NAMDRC annual meeting will be held March 23-25, 2017, at the Meritage Resort in Napa, California. A variety of excellent speakers and topics of interest to the pulmonary, sleep, and critical care medicine community will be presented, including presentations on the asthma-COPD overlap syndrome, pulmonary hypertension in interstitial lung disease, use of big-data in critical care medicine, cardiovascular risk in obstructive sleep apnea, as well as talks on ICD-10 coding, and updates on practice management and on regulatory topics in pulmonary, critical care, and sleep medicine. Finally, Dr. Mark Kelley, a visiting scholar at the Harvard Business School, will present a special lecture on "What do consumers really value in health care?" Meeting details and a registration form can be found at NAMDRC.org.


DR. ATWOOD

On the regulatory front, NAMDRC is having ongoing discussions with the Centers for Medicare & Medicaid Services about new proposed regulations regarding so-called site neutrality affecting outpatient facilities after November 2015. The issue at hand is when a health care facility purchases a physician practice and incorporates it as part of its hospital system and subsequently bills hospital outpatient rates for its services. CMS regulations posted in early November would prevent this practice if the outpatient service is more than 250 yards from the main hospital campus and was not billing as an outpatient service prior to Nov. 2, 2015. Congress instructed CMS to try and curtail the practice of hospital acquisition of physician practices where the hospital is subsequently able to bill Medicare for virtually identical services at notably higher payment rates. The CMS rule, now finalized (with a comment period), would have the effect of requiring hospitals that start new pulmonary rehab programs, or expand existing programs at new locations beyond the 250 yard threshold from the main hospital campus, to bill for the outpatient service at the physician fee schedule rate. That rate, notably lower than the hospital outpatient payment rate, would clearly stifle any growth or expansion of pulmonary rehab.

The costs of starting a pulmonary rehabilitation program are capital intensive and, generally, only hospitals can afford the start-up and ongoing costs, making pulmonary rehabilitation almost always a hospital service. Cost data from CMS demonstrate that the vast majority of billing for pulmonary rehab comes from hospitals and not from physician practices. By stopping the use of hospital-based clinic billing for new or expanded pulmonary rehabilitation services, this has the likely result of severely limiting the development of new pulmonary rehabilitation programs. If the new site of the rehabilitation program is more than 250 yards away, the hospital must bill under the physician fee schedule for reimbursement. No health care enterprise is likely to expand rehabilitation into new venues with such low reimbursement. The real shame in this scenario is that pulmonary rehabilitation is an effective and very low cost intervention for patients with COPD, and its future is largely being threatened by low reimbursement – making it unattractive for hospitals to open new programs in new space they may have purchased.

What is the fix? NAMDRC has discussed this problem with CMS, pointing out the large likely negative impact on pulmonary rehabilitation. We discussed a possible exemption for pulmonary rehabilitation. The final rule does afford an additional comment period, and we anticipate further discussions with CMS. It is also likely that the American Hospital Association, strongly opposed to this new rule, may seek a legislative fix.

A final area of activity is our ongoing discussion with CMS about updating the archaic guidelines created by CMS that govern how patients can be prescribed a bilevel positive airway pressure (PAP) therapy device for different forms of hypoventilation. The guidelines have been so complicated to follow that many clinicians, often at the request of a durable medical equipment company, have obtained home ventilators for patients for whom it was difficult to get a bilevel PAP. To be sure, hypoventilation disorders are complicated. The different patient types have somewhat different equipment pathways but all are overly complicated and are real barriers to getting these patients the necessary ventilatory equipment, which usually can be a bilevel PAP device. The home ventilator pathway has been easier to use to get therapy provided so many physicians have followed it, but it is also a lot more expensive. However, as of October 2015, CMS has effectively shut down the home ventilator pathway unless the patient has an indwelling invasive airway (i.e., a tracheotomy tube). NAMDRC, working with other sister societies, patient organizations, and others, has developed a strategy to oppose this draconian step. We hope to move CMS in a more rational direction regarding ventilator therapy for a variety of patients with hypoventilation. This work is complicated, but we are determined to do our utmost to bring a contemporary approach to this important area of therapy.

Take one section of the survey at a time

MOC *from page 1*

and to make the certification exam relevant to current clinical practice. The ABIM Pulmonary Medicine Board strongly encourages everyone to take the time to help direct the future of the MOC exam.

Diplomates can find the survey when they log into their respective homepages on the ABIM website at www.abim.org. The survey does not need to be completed in one sitting, but rather can be done one section at a time. It takes approximately 15 minutes to finish each section.

A link to the survey is located in the My Reminders tab.

This is a great opportunity for individuals to make their voices heard.

INPATIENT AND TRANSITIONAL CARE: PULMONARY DISEASE AND CRITICAL CARE MEDICINE *(13% of exam)*	Diagnosis	Testing	Treatment/ Care Decisions	Risk Assessment/ Prognosis/ Epidemiology	Pathophysiology/ Basic Science
OBSTRUCTIVE AIRWAY DISEASE *(2% of exam)*					
Asthma					
Allergic bronchopulmonary aspergillosis LF	⊘	⊘	⊘	⊗	⊗
Asthma mimics (including vocal cord dysfunction) LF	⊘	⊘	⊘	⊘	⊗
Acute asthma	✓	✓	✓	✓	⊘
Chronic bronchitis and emphysema	✓	✓	✓	✓	⊗
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) LF	⊘	⊘	⊗	⊗	⊗

✓ – ***High Importance***: *At least 75% of exam questions will address topics and tasks with this designation.*
⊘ – ***Medium Importance***: *No more than 25% of exam questions will address topics and tasks with this designation.*
⊗ – ***Low Importance***: *No exam questions will address topics and tasks with this designation.*
LF – ***Low Frequency***: *No more than 20% of exam questions will address topics with this designation, regardless of task or importance.*

MOC Blueprint Excerpt from the Hospital Medicine Examination

Can we count on you?

CHEST Foundation grant funding for the East African Training Initiative (EATI), for example, will help reduce mortality. Ethiopia bears the burden of high TB and lung disease prevalence. In a country of more than 94 million people, a single pulmonologist was tasked with providing treatment to critically ill patients in a 12-bed ICU. He was armed with a dilapidated facility that had no running water, two functioning ventilators, and no means of performing dialysis. There was no continuity of care at the ICU, and rounds were performed only during the week by rotating departments, few of which were trained in critical care.

This all started to change in 2013, when the EATI, a 2-year fellowship training program in pulmonary and critical care medicine, was launched. With the help of funding from a 2016 CHEST Foundation community service grant, the EATI is establishing infrastructure in Ethiopia to train fellows in pulmonary and critical care medicine for years to come. It is not relief work. The fellows graduating the program go on to set up ICUs in their own hospitals and universities. "As of now, we've already graduated five pulmonologists, and we are on track to graduate fifteen by the year 2020," explained Dr. Joseph Huang, Chairman of Fundraising for the EATI.

The drastic results of reduced mortality rates in the medical ICU have caught the attention of the Ethiopian Ministry of Health. By working directly with the EATI, the ministry established a task force in ICU medi-

Continued on following page

This month in *CHEST*

Editor's picks

BY RICHARD S. IRWIN, MD, MASTER FCCP

Editor In Chief, CHEST

Oral Macrolide Therapy Following Short-term Combination Antibiotic Treatment of *Mycobacterium massiliense* Lung Disease. *By Dr. Won-Jung Koh, et al.*

Impact of Acute Changes in CPAP Flow Route in Sleep Apnea Treatment. *By Dr. R. G. Andrade, et al.*

Endobronchial Ultrasound: Clinical Uses and Professional Reimbursements. *By Dr. T. R. Gildea and Dr. K. Nicolacakis.*

Chronic Cough Due to Gastroesophageal Reflux in Adults: CHEST Guideline and Expert Panel Report. *By Dr. P. J. Kahrilas, et al., on behalf of the CHEST Expert Cough Panel.*

Continued from previous page

cine with a goal to ultimately establish standard protocols in the nation's ICUs, using the EATI program as a model.

"The CHEST Foundation grant allows us to dive deeper into specialized training and also to sustain and expand the program. Because of this grant, we are able to do workshops on airway management, advanced bronchoscopy, chest tube insertion, and central lines," Dr. Huang explained.

Programs like the EATI are able to continue their work because of generous support from lung health champions like you. **Can we count on you to continue your support of the CHEST Foundation during this season of giving?** Your tax-deductible gift today will help us reach our goal of $2.5 million to support programs that are changing the future for patients with lung disease all over the world. You can make your gift at chestnet.org/donate or by calling the foundation staff at 224/521-9569.

As we celebrate our 20th Anniversary this year, we thank you for your steadfast support and dedication to the CHEST Foundation. The last 20 years of success would not have been possible without the tireless commitment of our generous donors and volunteers.

CRITICAL CARE COMMENTARY The 'big data' revolution and its relevance to critical care

BY MATTHEW CHURPEK, MD, PHD

According to IBM, over 2 quintillion bytes of data are generated every day (that's a 2 with 18 zeros!), with over 90% of the data in the world today generated in the past 2 years alone.

In our private lives, much of this information is generated through online shopping, web surfing, and popular websites such as Facebook and Twitter. Companies are making incredible efforts to collect these data and to use it to improve how they relate to customers and, ultimately, to make more money. For example, companies like Google, Amazon, Facebook, and Netflix collect enormous amounts of data and then use algorithms to provide real-time suggestions for what their customers might want to rent, buy, or click on. These algorithms, which companies use for anything from predicting customer behavior to facial recognition, were developed in the field of machine learning, a branch of computer science that focuses on how to learn from data.

Big data and critical care

Although the "big data" revolution has proliferated across the private sector, medicine has been slow to utilize the data we painstakingly collect in hospitals every day in order to improve patient care.

Clinicians typically rely on their intuition and the few clinical trials that their patients would have been included in to make decisions, and evidence-based clinical decision support tools are often not available or not used. The tools and scores we have at our disposal are often oversimplified so that they can be calculated by hand and usually rely on the clinician to manually gather information from the electronic health record (EHR) to calculate the score. However, this is starting to change. From partnerships between IBM Watson and hospitals, to groups developing and implementing clinical decision support tools in the EHR, it is clear that hospitals are becoming increasingly interested in learning from and using the enormous amount of data that are just sitting in the hospital records.


DR. CHURPEK

Although there are many areas in medicine that stand to benefit from harnessing the data available in the EHR to improve patient care, critical care should be one of the specialties that benefits the most. With the variety and frequency of monitoring that critically ill patients receive, there are large swaths of data available to collect, analyze, and harness to improve patient care. The current glut of information results in data overload and alarm fatigue for today's clinicians, but intelligent use of these data holds promise for making care safer and more efficient and effective.

Groups have already begun using these data to develop tools to identify patients with ARDS (Herasevich V, et al. *Intensive Care Med*. 2009;35[6]:1018-23), patients at risk of adverse drug reactions (Harinstein LM, et al. J Crit Care. 2012;27[3]:242-9), and those with sepsis (Tafelski S, et al. *J Int Med Res*. 2010;38:1605-16).

Furthermore, groups have begun "crowdsourcing" critical care problems by making large datasets publicly available, such as the Multi-parameter Intelligent Monitoring in Intensive Care (MIMIC) database, which now holds clinical data from over 40,000 ICU stays from Beth Israel Deaconess Medical Center. Continued efforts to utilize data from patients in the ICU have the potential to revolutionize the care in hospitals today.

Although the "big data" revolution has proliferated across the private sector, medicine has been slow to utilize the data we painstakingly collect in hospitals every day in order to improve patient care.

An important area of critical care that has seen a rapid rise in the use of EHR data to create decision support tools is in the early detection of critical illness. Given that many in-hospital cardiac arrests occur outside the ICU and delays in transferring critically ill patients to the ICU increase morbidity and mortality (Churpek MM, et al. *J Hosp Med*. 2016;11[11]:757-62), detecting critical illness early is incredibly important.

For millennia, clinicians have relied on their intuition and experience to determine which patients have a poor prognosis or need increased levels of care. In the 1990s, rapid response teams (RRTs) were developed, with the goal of identifying and treating critical illness earlier. Along with them came early warning scores, which are objective tools that typically use vital sign abnormalities to detect patients at high risk of clinical deterioration. RRTs and the early warning scores used to activate them have proliferated around the world, including in the United States, and scores like the Modified Early Warning Score (MEWS) are available for automatic calculation in the EHR.

However, taking a tool such as the MEWS that can easily be calculated by hand and making our expensive EHRs calculate it is a lot like buying a Ferrari just to drive it around the parking lot. There is no reason to limit our decision support tools to simple algorithms with only a few variables, especially when patients' lives are at stake.

Several groups around the country have, therefore, begun to utilize other variables in the EHR, such as laboratory values, to create integrated decision support tools for the early identification of critical illness. For example, Kollef and colleagues developed a statistical model to identify critical illness and implemented it on the wards to activate their RRT, which resulted in decreased lengths of stay in the intervention group (Kollef MH, et al. *J Hosp Med*. 2014;9[7]:424-9).

Escobar et al. developed a model to predict ICU transfer or non-DNR deaths in the Kaiser system and found it to be more accurate than the MEWS in a validation cohort (Escobar GJ, et al. *J Hosp Med*. 2012;7[5]:388-95). A clinical trial of their system is ongoing.

Finally, our group developed a model called eCART in a multicenter study of over 250,000 patients and has since implemented it in our hospital. An early "black-box" study found that eCART detected more patients who went on to experience a cardiac arrest or ICU transfer than our usual care RRT and it did so 24 hours earlier (Kang MA, et al. *Crit Care Med*. 2016;44[8]:1468-73). These

Continued on page 32

Editor's comment

Why should busy ICU clinicians bother with big data? Isn't this simply a "flash in the pan" phenomenon that has sprung up in the aftermath of the electronic medical records (EMRs) mandated by the Affordable Care Act? Are concerns valid that clinical data–based algorithms will lead to an endless stream of alerts akin to the ubiquitous pop-up ads for mortgage refinancing, herbal Viagra, and online gambling that has resulted from commercial data mining?

In this Critical Care Commentary, Dr. Matthew Churpek convincingly outlines the potential inherent in the big data generated by our collective ICUs. These benefits are manifesting themselves not just in the data populated within the EMR – but also in the novel ways we can now design and execute studies. And for those who aren't yet convinced, recall that payers already use the treasure trove of information within our EMRs against us in the forms of self-serving quality metrics, punitive reimbursement, and unvalidated hospital comparison sites.

Lee E. Morrow, MD, FCCP, is the editor of the Critical Care Commentary section of *CHEST Physician*.

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.

gsk

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]*.

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PULMONARY PERSPECTIVES

My journey into pulmonary-critical care medicine

BY SAMANTHA LEE, MD

Growing up was not easy. Camden, an inner city in southern New Jersey, is known for its abject poverty, constant violence, and drug trafficking and has been notoriously labeled as one of the "most dangerous cities in the US." It is a daunting place for many, but home for me. My story is one of a single mother high school dropout with eight children, who worked tirelessly to provide my siblings and me with more advantageous circumstances than she had.

I wanted nothing more than to graduate high school, so I vowed early on to make this a reality. With that commitment, I graduated from high school at the top of my class, later also graduating with honors as an undergraduate from the Indiana University of Pennsylvania. Looking back, I don't think I quite understood that my single vow to obtain a high school diploma would blossom into a burning desire to become a pulmonary-critical care doctor.

Courtesy Dr. Samantha Lee

Dr. Samantha Lee graduated from American University of Antigua College of Medicine in 2014.

They say "home is where the heart is." I guess this old statement holds true in my case when I think of why I choose to return to Camden for my residency training at Cooper Hospital. Driving to work in Camden is always a memorable event for me. With every corner and bend in the city, I get a short trip down memory lane. I remember fondly walking to the corner store to buy candy with quarters that my sisters and I dredged up from our couch cushions.

Sundays were my favorite days growing up. We all woke up very early with the singular purpose of getting ready for church. As a child, I loved the attention we all gave each other, especially on Sundays. My siblings and I squabbled and played pranks on each other all morning to my mother's displeasure, but, somehow, we always made it to church on time, dressed in our Sunday best. After church, our home was filled with hours of laughter, good food, and games only children knew how to play. Our house was always a second home to other kids from our block and friends of my mother who stopped by to try her famous chicken dishes. The days always had the feel of a fun holiday, like Halloween, or Christmas without the lights. It is important that people don't see Camden as a stereotype, as it has more to offer than murder stories, stray cats, and drug dealing. I am a product of this city.

As I got older, our days became very different. My mother had a hard time making ends meet despite working long hours at the local restaurant. I didn't see her much. My older siblings were always busy working, which likely led to their decision to drop out of high school early on. My mother was devastated by their decision, and I knew I couldn't let her down and follow that trend. One day I realized if I didn't take control of my life and focus on my education, I, too, would slip through the cracks. From that moment on, I took my future very seriously. I wanted something different. I invested all of my energy into school and my part-time job at the mall. I had a dream that started with me wanting only a high school diploma, which evolved into me becoming an internal medicine doctor.

Embarking on pulmonary-critical care medicine is my next chapter. I see the scourge of pulmonary disease in my internal medicine clinic and am looking forward to arming myself with the knowledge to ease my patients' burdens. Furthermore, I relish the opportunity to learn how to organize a chaos-filled room into an efficient, harmonized resuscitation situation. The process encourages teamwork, mindfulness, and empathy while being a scientist for the sickest patients in the hospital. These are all fundamental qualities I've strived to develop over my maturation as an internal medicine resident and traits I've also gained through my various life experiences. I am certain that no other field of medicine would better position me to serve in the broadest sense as a clinician, and I am sure that my life experiences will complement my scientific skill set.

It is said that a journey of a thousand miles begins with a single step. Who knew that someday, I would be able to help repay Camden for nurturing me as a child. I am ready for my new challenges and to embark on this new, pulmonary-critical care medicine chapter in my life.

Dr. Lee is an internal medicine resident at Cooper University Hospital at Cooper Medical School of Rowan University, Camden, NJ.

Editor's Note

Dr. Lee's thoughtful piece about why she chose to go into pulmonary–critical care medicine is both inspiring and insightful. She deserves commendation for her willingness to share her story, and I am humbled by her words.

Nitin Puri, MD, FCCP, is the editor of the Pulmonary Perspectives section of CHEST Physician.

Continued from page 27

scores and many more will likely become commonplace in hospitals to provide an objective and accurate way to identify critically ill patients earlier, which may result in decreased preventable morbidity and mortality.

Future directions

There are several important future directions at the intersection of big data and critical care. First, efforts to collect, store, and share the highly granular data in the ICU are paramount for successful and generalizable research collaborations. Although there are often institutional barriers to data sharing to surmount, efforts such as the MIMIC database provide a roadmap for how ICU data can be shared and problems "crowdsourced" in order to allow researchers access to these data for high quality research.

Second, efforts to fuse randomized controlled trials with big data, such as randomized, embedded, multifactorial, adaptive platform (REMAP) trials, have the potential to greatly enhance the way trials are done in the future. REMAP trials would be embedded in the EHR, provide the ability to study multiple therapies at once, and adapt the randomization scheme to ensure that patients are not harmed by interventions that are clearly detrimental while the study is ongoing (Angus DC. *JAMA*. 2015;314[8]:767-8).

Finally, it is important that we move beyond the classic statistical methods that are commonly used to develop decision support tools and increase our use of more modern machine learning techniques that companies in the private sector use every day. For example, our group found that classic regression methods were the least accurate of all the methods we studied for detecting clinical deterioration on the wards (Churpek MM, et al. *Crit Care Med*. 2016;44[2]:368-74). In the future, methods such as the random forest and neural network should become commonplace in the critical care literature.

The big data revolution is here, both in our private lives and in the hospital. The future will bring continued efforts to use data to identify critical illness earlier, improve the care of patients in the ICU, and implement smarter and more efficient clinical trials. This should rapidly increase the generation and utilization of new knowledge and will have a profound impact on the way we care for critically ill patients.

Dr. Churpek is assistant professor, section of pulmonary and critical care medicine, department of medicine at University of Chicago.

Hypervirulent *Mycobacterium* infecting CF patients

BY MICHELE G. SULLIVAN
Frontline Medical News

A recently evolved strain of *Mycobacterium* is circulating in hospitals worldwide, causing nearly impossible-to-treat lung infections among patients with cystic fibrosis.

A genome-wide study has determined that *Mycobacterium abscessus* is not transmitted through soil and water, as once thought, but is a nosocomial infection transmitted person to person through droplet and surface contamination, Andres Floto, MD, reported in Science (2016 Nov 11;354[6313]:751-7).

"The bug initially seems to have entered the patient population from the environment, but we think it has recently evolved to become capable of jumping from patient to patient, getting more virulent as it does so," Dr. Floto of the University of Cambridge, England, wrote in a press statement.

The path of global transmission is not yet entirely clear, the authors noted. But since it first appeared, around 1978, *M. abscessus* has spread globally, strongly suggesting that asymptomatic carriers may be one source of transmission.

"We found no evidence of cystic fibrosis patients or of equipment moving between centers in different countries, indicating that the global spread of *M. abscessus* may be driven by alternative human, zoonotic, or environmental vectors of transmission," the researchers wrote.

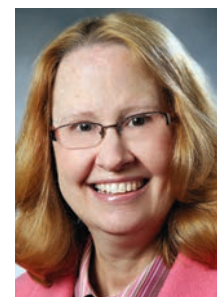
The team conducted whole-genome sequencing

Continued on following page

VIEW ON THE NEWS

CF patients need conscientious infection control

Approximately 30,000 American adults, children, and infants have cystic fibrosis. Nontuberculous mycobacteria (NTM) are ubiquitous environmental microorganisms, and it has been known for some time that these infections can be transmitted person to person. Any patient, actually, who has preexisting lung disease – and especially those with poor mucociliary clearance – are at risk for a nontuberculous mycobacterial infection. This type of lung infection also can be difficult to diagnose and hard to treat. The U.S. Cystic Fibrosis Foundation in conjunction with the European Cystic Fibrosis Society has developed consensus guidelines for infection control, evaluation, and treatment of this problem. This executive summary was published last January (Floto et al. Thorax.2016;71:i1-i22).



Specifically for nontuberculous mycobacteria, it is recommended to see patients in CF clinic and admit patients to the hospital in an "airborne infection isolation room (AIIR)" if NTM is suspected and until *M. tuberculosis* is ruled out. These AIIRs use engineering controls to prevent airborne transmission of infectious agents that remain suspended in the air and travel long distances along air currents. Rooms that have been renovated or constructed prior to 2001 must have at least six air exchanges per hour and those renovated or constructed since 2001 must at least 12 air exchanges per hour. These rooms should be under negative pressure. Also, even though in a negative pressure room, the patient will be under contact precautions: anyone entering must be gowned, gloved, and wearing an N95 respirator.

At our center, in addition to the standard contact precautions we use for every CF patient, patients with confirmed NTM infections are seen at every clinic visit in an airborne infection isolation room. We also require all CF patients to wear an isolation mask when entering the hospital or clinic facility, when going to a laboratory, or even when going to the bathroom down the hall. Finally, we stress the significant importance of good hand hygiene.

Susan Millard, MD, FCCP, is a pediatric pulmonologist with Spectrum Health/Butterworth Hospital in Grand Rapids, Mich.

Continued from previous page

on 1,080 samples of *M. abscessus* obtained from 517 cystic fibrosis patients in clinics and hospitals within the United States, the United Kingdom, Europe, and Australia. They identified three subspecies, some of which contained nearly genetically identical strains, "suggesting widespread transmission of circulating clones within the global cystic fibrosis patient community."

Most patients (74%) were infected with these genetically identical strains despite their diverse geographic locations. The isolates were amazingly similar, the authors noted:

"The bug initially seems to have entered the patient population from the environment, but we think it has recently evolved to become capable of jumping from patient to patient, getting more virulent as it does so."

90% differed by less than 20 single nucleotide polymorphisms.

Using these strains, the researchers were able to construct several possible transmission chains in most of the cystic fibrosis centers included in the study. The three dominant circulating clones were all observed in the United States, European, and Australian samples, indicating transcontinental transmission.

"We also detected numerous examples of identical or near-identical isolates infecting groups of patients in different cystic fibrosis centers and, indeed, across different countries, indicating the recent global spread of *M. abscessus* clones throughout the international cystic fibrosis patient community."

The team also determined that the common ancestor of these strains probably emerged around 1978.

Another sequencing series tracked specific isolates among individual patients. This strongly suggests person-to-person transmission. Adding this to their previous work on *M. abscessus* transmission, the authors postulated that spread was probably by surface contamination by droplet contamination and by cough aerosol from infected patients.

The team then looked at clinical outcomes associated with the bacteria and treatment with amikacin and macrolides – antibiotics typically used to fight this very-challenging infection. "We did observe increased rates of chronic infection in individuals," infected with the clones, which were resistant to both those medications, they said.

In immunodeficient mice, the strains were more likely to cause granulomatous and inflammatory lung changes. And the bacteria tended to survive even after being consumed by macrophages, "suggesting that the establishment of transmission chains may have permitted multiple rounds of within-host genetic adaptation to allow *M. abscessus* to evolve from an environmental organism to a true lung pathogen."

The research was funded by the Wellcome Trust and the Cystic Fibrosis Trust in the United Kingdom.

There were no financial disclosures.

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LABA/LAMA again a winner at treating COPD

BY DOUG BRUNK
Frontline Medical News

EXPERT ANALYSIS AT CHEST 2016

LOS ANGELES – Indacaterol/glycopyrronium was superior to salmeterol/fluticasone at reducing the risk and rate of moderate to severe exacerbations in chronic obstructive pulmonary disease (COPD) patients with more than one or zero to one exacerbations in the previous year, results from an indirect comparison showed.

"Acute exacerbations of COPD are associated with accelerated decline in lung function and increased mortality," Kenneth R. Chapman, MD, FCCP, said at the annual meeting of the American College of Chest Physicians. "Current GOLD [Global Initiative for Chronic Obstructive Lung Disease] strategy recommends

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LABA/ICS [long-acting beta-agonist/inhaled corticosteroid] combination, and/or LAMA [long-acting muscarinic antagonist] as the first-line treatment, and LABA/LAMA as an alternative treatment for COPD patients at a high risk of exacerbations."

In an effort to examine the reduction in moderate or severe exacerbations in COPD patients taking indacaterol/glycopyrronium (a combination of a LABA bronchodilator and a LAMA bronchodilator) or salmeterol/fluticasone (a LABA and inhaled glucocorticoid combination), researchers compared results from the FLAME and LANTERN trials. The FLAME study evaluated the rate and risk of exacerbations with indacaterol/glycopyrronium versus salmeterol/fluticasone in 3,362 moderate to very severe COPD patients with at least one exacerbation in the previous year (N Engl J Med. 2016;374[23]:2222-34). The LANTERN study compared the efficacy and safety of indacaterol/glycopyrronium versus salmeterol/fluticasone in 744 moderate to very severe COPD patients with 0-1 exacerbation in the previous year (Int J Chron Obstruct Pulmon Dis. 2015;10:1015-26).

Dr. Chapman, professor of medicine at the University of Toronto, reported that, in the FLAME study, which was 52 weeks long, indacaterol/glycopyrronium significantly reduced the annualized rate of moderate or severe COPD exacerbations in patients who had one or more exacerbation in the previous year (a rate ratio of 0.83; *P* less than 0.001), which translated into a clinically meaningful 17% reduction, compared with their counterparts taking salmeterol/fluticasone.

Doug Brunk/Frontline Medical News

LABA/LAMA can be considered the preferred treatment, Dr. Chapman said.

In the LANTERN study, which was 26 weeks long, indacaterol/glycopyrronium also significantly reduced the annualized rate of patients who had 0-1 exacerbation in the previous year, compared with those taking salmeterol/fluticasone (RR, 0.69; $P = .048$).

In FLAME, indacaterol/glycopyrronium significantly delayed the time to first moderate or severe exacerbation, with a clinically meaningful 22% risk reduction, compared with salmeterol/fluticasone (hazard ratio, 0.78; *P* less than .001). Similar findings were observed in LANTERN; indacaterol/glycopyrronium significantly delayed the time to first moderate or severe exacerbation, with a clinically meaningful 35% risk reduction, compared with salmeterol/fluticasone (HR, 0.65; *P* less than .028).

"These results suggest that LABA/LAMA combinations such as indacaterol/glycopyrronium can be considered as a preferred treatment option in the management of COPD patients, irrespective of exacerbation history," Dr. Chapman said. He reported having numerous financial disclosures.

dbrunk@frontlinemedcom.com

Bleeding upped when on antiplatelets during EBUS

BY M. ALEXANDER OTTO
Frontline Medical News

AT CHEST 2016

LOS ANGELES – There might be a slight increase in delayed bleeding when patients have endobronchial ultrasound (EBUS) with transbronchial needle aspiration within 5 days of taking oral antiplatelets, according to a review of 404 patients at Riverside Methodist Hospital in Columbus, Ohio.

This study is unusual in that it looked at the 48 hour mark. Previous studies have tended to focus on immediate bleeding events that require the procedure to be stopped; only some of that research has found an increased bleeding risk with antiplatelet therapy.

In the study at Riverside Methodist, none of the 20 patients on dual antiplatelet therapy – clopidogrel (Plavix) plus aspirin – bled during the procedure, but one (5%) had a hemoglobin drop of more than 2 g within 48 hours and another was readmitted to the hospital within 48 hours for procedure-related hemoptysis. Overall, the delayed bleeding event rate for patients using the dual antiplatelet therapy was 10%. Additionally, one of the 13 patients (7.7%) on clopidogrel alone experienced a greater than 2 g drop in hemoglobin.

Among the 270 patients not exposed to antiplatelets, the overall bleeding event rate was 2.6%, and the event rate for delayed bleeding was 1.1%. Four patients (1.5%) bled during the procedure, two (0.7%) had hemoglobin drops greater than 2 g within 48 hours, and one (0.4%) was readmitted for hemoptysis.

There were no bleeding events in 101 patients who took only aspirin.

"There was a trend toward delayed bleeding events in patients" on clopidogrel or dual antiplatelets. "It's worth considering a thoughtful pause in decision making. Maybe with the bleeding events we're seeing, it would be worthwhile, if possible, to defer" EBUS with transbronchial needle aspiration "until after the antiplatelet therapy," said Kevin Swiatek, DO, a medicine resident at Riverside, at the annual meeting of the American College of Chest Physicians.

Patients were excluded from the study if they had histories of bleeding or clotting disorders; low platelet counts; or if they were on anticoagulation. Subjects on antiplatelets were about 10 years older, on average, than those who were not (about 68 versus 59 years old), and more likely to have had a heart attack or stroke, and to be hypertensive.

There was no industry funding for the work, and the investigators had no disclosures.

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Comorbidities common in COPD patients

BY DOUG BRUNK
Frontline Medical News

AT CHEST 2016

LOS ANGELES – Comorbidities are common in patients with chronic obstructive pulmonary disease, especially cardiovascular disease, diabetes, anemia, and osteoporosis, results from a single-center analysis showed.

"These affect the course and outcome of COPD, so identification and treatment of these comorbidities are very important," Hamdy Mohammadien, MD, FCCP, said in an interview in advance of the annual meeting of the American College of Chest Physicians.

In an effort to estimate the presence of comorbidities in patients with COPD and to assess the relationship of comorbid diseases with age, sex, C-reactive protein, and COPD severity, Dr. Mohammadien and his associates at Sohag (Egypt) University, retrospectively evaluated 400 COPD patients who were at least 40 years of age. Those who presented with bronchial asthma or other lung diseases were excluded from the analysis. The mean age of patients was 62 years, 69% were male, and 36% were current smokers. Their mean FEV_1/FVC ratio (forced expiratory volume in 1 second/forced vital capacity) was 48%, and 57% had two or more exacerbations in the previous year.

Dr. Mohammadien reported that all patients had at least one comorbidity. The most common comorbidities were cardiovascular diseases (85%), diabetes (35%), dyslipidemia (23%), osteopenia (11%), anemia (10%), muscle wasting (9%), pneumonia (7%), osteoporosis (6%), GERD (2%), and lung cancer (2%). He also noted that the association between cardiovascular events, dyslipidemia, diabetes, osteoporosis, muscle wasting, and anemia was highly significant in COPD patients aged 60 years and older, in men, and in patients with stage III and IV COPD. In addition, a significant relationship was observed between a positive CRP level and each comorbidity, with the exception of gastroesophageal reflux disease and lung cancer. The three comorbidities with the greatest significance were ischemic heart disease ($P = .0001$), dyslipidemia ($P = .0001$), and pneumonia ($P = .0003$). Finally, frequent exacerbators were significantly more likely to have two or more comorbidities (odds ratio 2; $P = .04$) and to have more hospitalizations in the past year (P less than .01).

"Comorbidities are common in patients with COPD, and have a significant impact on health status and prognosis, thus justifying the need for a comprehensive and integrating therapeutic approach," said Dr. Mohammadien, who reported no conflicts of interest, at the meeting.

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SOFA best predicted in-hospital mortality in acute COPD

BY DOUG BRUNK
Frontline Medical News

AT CHEST 2016

LOS ANGELES – The Sequential Organ Failure Assessment (SOFA) score and the Glasgow Coma Scale (GCS) are simple, accurate tools for risk stratification of hospitalized patients with acute exacerbation of COPD, results from a single-center study showed.

"Acute exacerbations of chronic obstructive pulmonary disease often require hospitalization, may necessitate mechanical ventilation, and can be fatal," Mohamed Metwally, MD, FCCP, said in an interview in advance of the annual meeting of the American College of Chest Physicians. "There are currently no validated disease-specific scores that measure the severity of acute exacerbation. Prognostic tools are needed to assess acute exacerbations of chronic obstructive pulmonary disease."


DOUG BRUNK/FRONTLINE MEDICAL NEWS

Dr. Mohamed Metwally at the CHEST annual meeting.

Dr. Metwally of Assiut (Egypt) University Hospital noted that scoring models were first introduced for critically ill patients in the ICU in 1980 and subsequently developed for heterogeneous ICU populations, but have not been used to study risk prediction in COPD patients. The purpose of the current trial was to evaluate and compare the performance of general scoring systems commonly used in general ICUs to accurately predict outcomes in hospitalized patients with acute exacerbation of COPD (AECOPD).

For the 2-year study, Dr. Metwally and his associates prospectively evaluated 250 critically ill ICU AECOPD patients, mean age 65 years, at Assiut University Hospital between December 2012 and December 2014. The primary outcome was in-hospital mortality while the secondary endpoint was need for intubation and mechanical ventilation. The researchers excluded patients who died less than 24 hours after admission, those with underlying COPD who were admitted with another primary diagnosis such as an accident or a stroke, or for elective hospitalizations such as elective surgery or diagnostic procedures.

Dr. Metwally and his associates collected sociodemographic data, vital signs, and other clinical

Continued on following page

Continued from previous page

variables, and collected scores from five tools used to measure mortality prediction: the Acute Physiology and Chronic Health Evaluation (APACHE II), the SOFA score, the Early Warning Score (EWS), the GCS, and the Charlson Comorbidity Index (CCI). To assess performance of the scores, they used area under the receiver operating characteristic curve (AUC) analysis and the Hosmer-Lemeshow goodness-of-fit test for logistic regression.

Of the 250 patients, 43 (17%) died during their hospital stay and 54% required mechanical ventilation. All recorded scores were significantly higher in nonsurvivors, compared with survivors, and the risk of clinical deterioration increased with increasing scores. The discriminatory power of each score varied as measured by AUC analysis. The AUC of APACHE II, SOFA, EWS, GCS, and CCI were 0.79, 0.81, 0.76, 0.69, and 0.68, respectively "and all these models had good calibration in mortality prediction," Dr. Metwally said. The SOFA score was the best in predicting mortality (its predicted mortality was 16%, compared with the actual mortality of 17%), while the APACHE II score overestimated mortality by at least twofold (46% vs. 17%). In addition, the EWS outperformed the GCS in predicting mortality. "This may be due to EWS containing all vital signs plus level of consciousness," he said in an interview.

The GCS was found to be the most useful in predicting need for mechanical ventilation, with an AUC of 0.81. The AUCs of APACHE II, SOFA, EWS, and CCI were 0.79, 0.80, 0.73, and 0.61, respectively. All of the scores had good calibration in mortality prediction, Dr. Metwally said, with the exception of SOFA.

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LABA withdrawal does not worsen asthma control

BY SARA FREEMAN
Frontline Medical News

LONDON – Real-life experience shows that stopping treatment with a long-acting beta-agonist (LABA) does not worsen asthma control, nor does it lead to any immediate decline in lung function.

Spirometric parameters were similar before and 3 weeks after stopping LABA therapy in an observational study of 58 patients who had stable asthma and were being treated with an inhaled corticosteroid (ICS) and a LABA.

The forced expiratory volume in 1 second (FEV_1) was 88.8% at baseline and 89.5% at the 3-week visit after stepping down their LABA therapy ($P = .55$). Patients' average peak expiratory flow rate was 462 L/min both before and after LABA withdrawal.

In addition, no changes were seen in lung function based on impulse oscillometry, a noninvasive method for measuring airway resistance and reactance (Chest. 2014;146[3]:841-7). Similar levels of fractional exhaled nitric oxide (FeNO, 38 and 36 ppb) were recorded.

The findings were presented at the annual congress of the European Respiratory Society (ERS) and have been published in an early online edition of the Annals of Allergy, Asthma & Immunology (doi: 10.1016/j.anai.2016.07.022).

About 45% of the UK adult asthma population are taking step 3 GINA [Global Initiative for Asthma] therapy, which is ICS/LABA, said Sunny Jabbal, MD, of the Scottish Centre for Respiratory Research at Ninewells Hospital in Dundee, where the study was conducted. Patients should be on the lowest of the five steps in the 2016 GINA guidelines that achieve asthma control and should be regularly reviewed.

To test whether the LABA could be safely withdrawn, that is stepped down to ICS only [GINA step 2], Dr. Jabbal and his colleagues studied 58 patients with a mean age of 39 years. All had well-controlled asthma, and had been receiving ICS/LABA for at least 3 months with no asthma exacerbations requiring treatment. None of the patients were current smokers.

At study entry, patients underwent spirometry, impulse oscillometry, and had FeNO measured. Their LABA was then stopped, and patients were reassessed 3 weeks later. In accordance with GINA, their ICS dose was also reduced by approximately 25%," Dr. Jabbal said. Patients recorded their symptoms and short-term reliever (albuterol) use on simple diary cards. No adverse events were reported. The mean daily symptom score recorded during the step down process was 0.4, and the mean albuterol usage was one puff per day.

Asthma-COPD overlap syndrome gets missed

BY M. ALEXANDER OTTO
Frontline Medical News

Exacerbations in bronchodilator-responsive asthma–COPD overlap syndrome (ACOS) were more frequent and severe than in chronic obstructive pulmonary disease with emphysema, but only a minority of patients were treated to prevent them, in a review of 1,005 patients from the Annals of the American Thoracic Society.

All subjects were current or former smokers culled from the COPDGene Study, a multicenter observational study looking for the genetic roots of COPD susceptibility; 385 patients met the investigators' criteria for ACOS with bronchodilator response (ACOS-BDR), which included a history of asthma or hay fever, airway obstruction with significant bronchodilator responsiveness, and less than 15% emphysema on chest CT.

Another 620 subjects met criteria for COPD with emphysema, including airway obstruction without bronchodilator reversibility, and more than 15% emphysema on chest CT (Ann Am Thorac Soc. 2016 Sep;13[9]:1483-9).

Although the ACOS patients had better lung function, they had similar severity and frequency of exacerbations, compared with the COPD group. After adjustment for forced expiratory volume in 1 second (FEV_1) percent predicted and other factors, the patients with ACOS-BDR were actually more likely to have severe and frequent exacerbations. Possible explanations for this are that they were more likely to smoke and have gastroesophageal reflux disease and obstructive sleep apnea, all of which increase the risk of exacerbations.

Even so, ACOS-BDR patients were less likely to be on a long-acting beta-agonist (6.8% vs. 13.9%); a long-acting muscarinic antagonist (20% vs. 60.8%); or a combination long-acting beta-agonist/inhaled corticosteroid (29.9% vs. 55.6%).

"Only a small percentage of them were being treated ... Early and aggressive treatment with combination therapy may help alleviate symptoms and decrease exacerbations," said investigators led by James Cosentino, DO, of Temple University, Philadelphia. Patients with ACOS "are a particularly high-risk group." They deserve "special attention, and practitioners need to be diligent in evaluation of them."

ACOS is being increasingly recognized as a distinct clinical entity with perhaps a worse prognosis than either asthma or COPD alone. The goal of the study was to better characterize the disease.

After adjustment for forced expiratory volume in 1 second (FEV_1) percent predicted and other factors, the patients with ACOS-BDR were actually more likely to have severe and frequent exacerbations.

To that end, the team found four features that seemed to distinguish ACOS-BDR from COPD with emphysema: ACOS-BDR patients were younger (60.6 vs. 65.9 years old); heavier (body mass index 29.6 vs. 25.1 kg/m^2; more likely to be African American (26.8% vs. 14.4%); and more likely to be current smokers (50.9% vs. 20.7%).

It's "likely that current smoking in subjects with ACOS, coupled with the long duration of asthma, leads to inflammation and small airway remodeling with development of symptoms earlier in the disease course than that seen in those with COPD with emphysema," the investigators said.

"Early and aggressive treatment with combination therapy may help alleviate symptoms and decrease exacerbations. Recognition and treatment of comorbidities and aggressive smoking cessation may also play a key role in preventing exacerbations and alleviating the morbidity associated with ACOS; however, future studies on the treatment of ACOS are needed," they said.

The majority of subjects with ACOS-BDR met criteria for Global Initiative for Chronic Obstructive Lung Disease grade B, indicating a high degree of symptoms despite less severe airflow obstruction.

Dr. Cosentino had no conflicts. Other authors disclosed personal fees from Concert Pharmaceuticals, CSA Medical, CSL Behring, Gala Therapeutics, and Novartis.

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VIEW ON THE NEWS

Call it all obstructive airway disease

The importance of this study is that it used readily available metrics to define ACOS in a COPD population. Although diffusion capacity was not reported, quantification of emphysema on chest CT scans combined with history and spirometry provide a reasonable approach to distinguishing ACOS-BDR from COPD with emphysema.

Although subjects with COPD had smoked more heavily as measured by cigarette pack-years, subjects with ACOS were much more likely to be current smokers. ... Subjects with ACOS also had a higher prevalence of comorbidities such as sleep apnea, diabetes mellitus, hypertension, and hypercholesterolemia as compared with patients with COPD. Having a higher body mass index, to near obesity, and a greater prevalence of gastroesophageal reflux disease raises questions related to diet, lifestyle, and nutrition as potential contributors to ACOS pathophysiology.

In the future, the use of diagnostic terms such as "asthma," "COPD," and "ACOS," will likely give way to the more unifying diagnosis of obstructive airway disease (OAD) ... OAD would be further delineated on the basis of molecular phenotyping, genomic, and systems biology approaches, in combination with more traditional clinical and physiological parameters. ... This new mindset can help us solve the problem of obstructive airway disease taxonomy and develop not only better treatments, but eventually invent lasting cures – if we are so lucky.

Amir Zeki, MD, is an assistant professor in the division of pulmonary, critical care, and sleep medicine at the University of California, Davis. Dr. Zeki had no disclosures. Nizar Jarjour, MD, is a professor of medicine and head of the allergy, pulmonary, and critical care division at the University of Wisconsin, Madison. Dr. Jarjour reported consulting fees from AstraZeneca, Daiichi Sankyo, and Teva. They made their comments in an editorial (Ann Am Thorac Soc. 2016 Sep;13[9]:1440-2).

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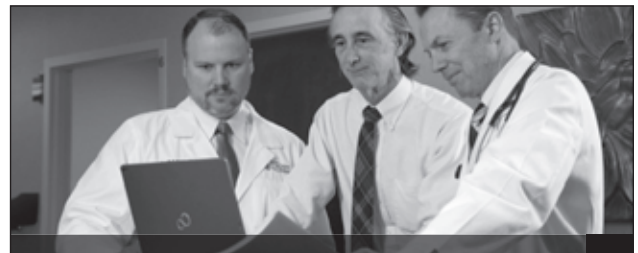

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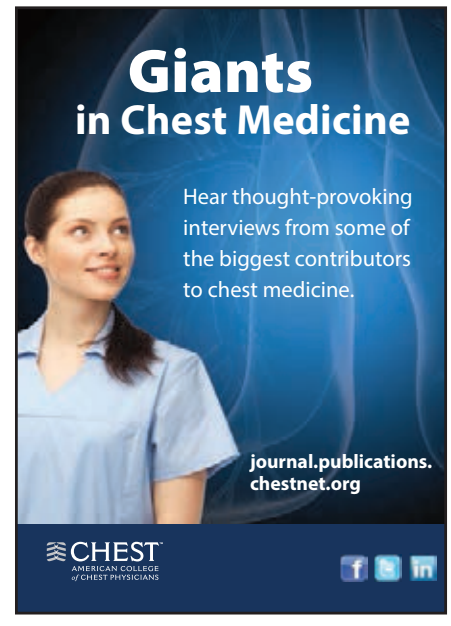

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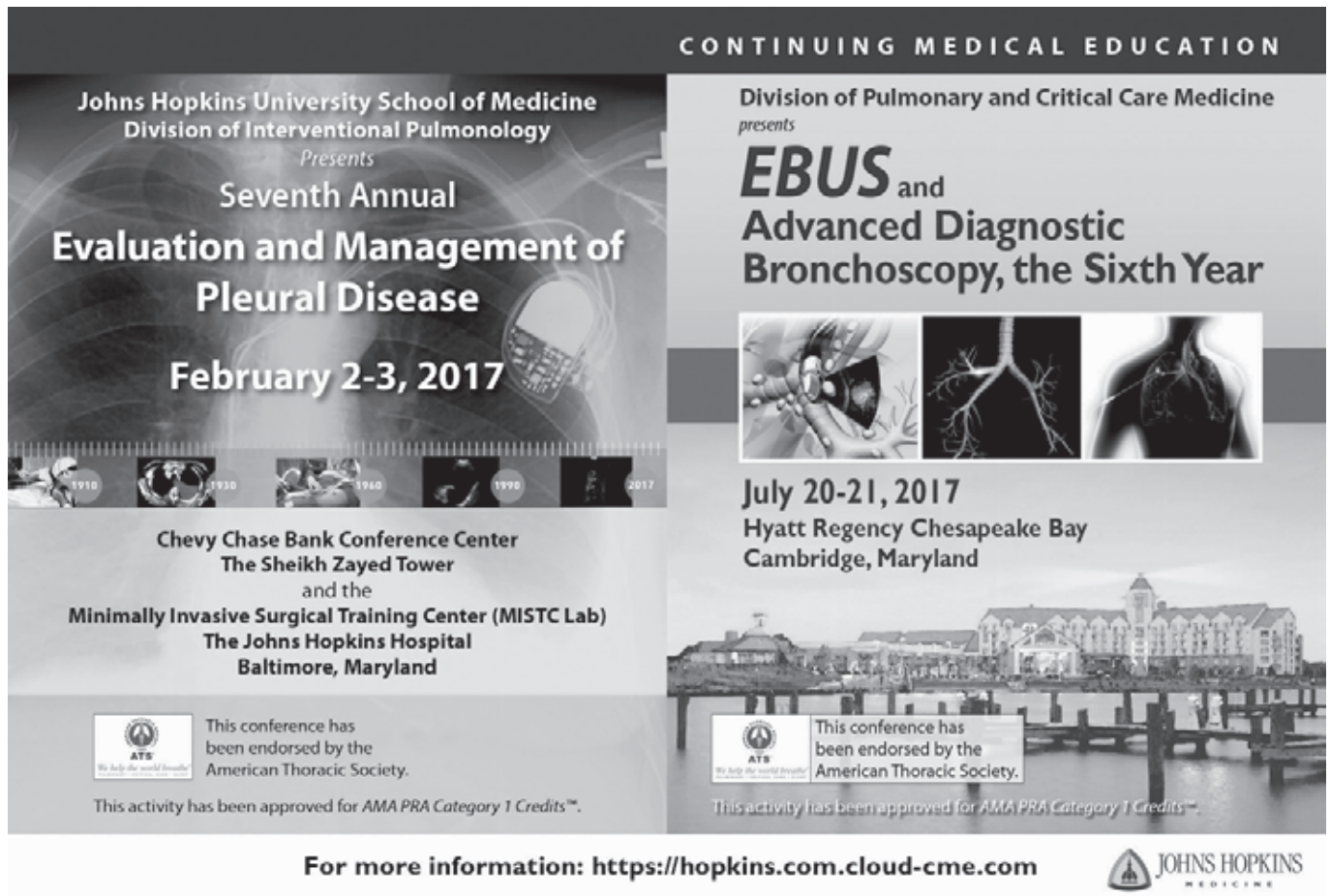


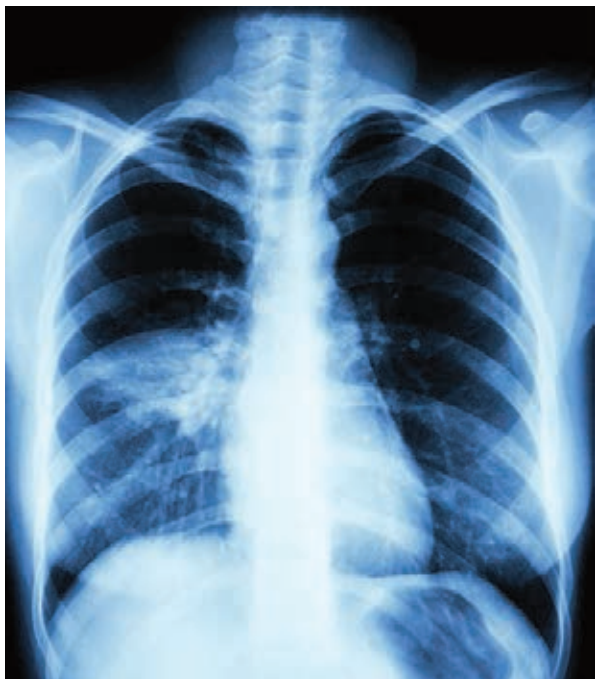
Few pneumonia incidents with ICS/LABA combo

BY SARA FREEMAN
Frontline Medical News

LONDON – The benefit of a fixed-dose inhaled corticosteroid (ICS) and long-acting beta-agonist (LABA) combination in reducing exacerbations of chronic obstructive pulmonary disease (COPD) far outweighed any risk for pneumonia in a post hoc analysis of the 48-week FORWARD study.

Although there were 13 extra pneumonia events when a fixed-dose combination of beclometasone diproprionate and formoterol fumarate (Foster, Chiesi Farmaceutici SpA) was used, as compared with formoterol fumarate alone, there were 123 fewer moderate to severe COPD exacerbations over a 342-day analysis period.

"Analysis of pneumonia and exacerbation cumulative number of events shows that the number of incident pneumonia remains very small relative to that of moderate to severe exacerbations," Massimo Corradi, MD, of the University of Parma (Italy), reported at the annual congress of the European Respiratory Society.



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Dr. Corradi added that the new analysis confirms that the ICS/LABA combination has a "positive risk-benefit balance over LABA monotherapy, supporting [the argument that] the benefits of adding an ICS to a bronchodilator significantly outweigh potential risks."

The FORWARD study was a two-arm trial designed to compare the efficacy and safety of fixed-dose treatment with beclometasone diproprionate and formoterol fumarate versus formoterol fumarate alone in 1,199 patients with severe COPD.

For inclusion in the study, patients had to have a post-bronchodilator forced expiratory volume in 1 second below 50% of predicted and a forced vital capacity ratio of less than 0.7. They also had to have a smoking history of 10 pack-years or more, and a history of at least one COPD exacerbation in the previous 12 months that had required treatment or hospitalization (Eur Respir J. 2013;41[1]:12-7).

After a 2-week run-in period, where all patients received a 24-mcg dose of formoterol fumarate, patients were randomized to continue treatment with formoterol fumarate or to receive the fixed-dose combination of beclometasone diproprionate 400 mcg and beclometasone diproprionate 24 mcg for 48 weeks.

A total of 1,186 patients, most of whom were male (69%) with a mean age of 64 years, formed the intention-to-treat population.

Published results (Respir Med. 2014;108[8]:1153-62) showed that the combination of the ICS beclometasone diproprionate and the LABA formoterol fumarate (Chiesi Farmaceutici SpA) was associated with a 28% reduction in the annual rate of moderate to severe exacerbations versus the LABA alone.

The adjusted rate of exacerbations per patient per year was 0.80 in patients treated with the ICS/LABA combination versus 1.12 for those treated with just the LABA, with an adjusted rate ratio of 0.72 (*P* less than .001).

The published data also showed that pneumonia was reported by 23 patients (3.8%) treated with the ICS/LABA and by 11 (1.8%) treated with the LABA only.

For the new analysis, Dr. Corradi and his coinvestigators looked at the cases of pneumonia and COPD exacerbations in more detail, plotting out the cumulative number of events over time and also characterizing the types of pneumonia in more detail.

All patients had a chest x-ray to confirm the presence of pneumonia, he said, noting that overall there were 35 cases of pneumonia, 24 occurring in patients treated with the fixed-dose beclometasone diproprionate and formoterol fumarate combination and 11 in patients treated only with formoterol fumarate.

Of these cases, 25 required in-hospital treatment – 16 patients in the ICS/LABA arm and 9 in the LABA-only arm. There were three instances of patients acquiring pneumonia in hospital – two in the ICS/LABA and one in the LABA-only arm.

There were also two fatal cases of pneumonia – one in each treatment group. Neither were thought to be related to either of the treatments.

These findings are in line with a recent review of the use of ICS for COPD by the European Medicines Agency (EMA/488280/2016), which noted that "overall the benefits of inhaled corticosteroid medicines in treating COPD continue to outweigh their risks and there should be no change to the way in which these medicines are used."

The European Medicines Agency advised that patients and clinicians need to "be alert for signs and symptoms of pneumonia, bearing in mind that the clinical features of pneumonia overlap with those of a worsening (exacerbation) of the underlying disease."

Dr. Corradi has received speaker fees from Chiesi Farmaceutici SpA, which funded the FORWARD study, and his coauthors are employees of the company.

Optimal management of GERD in IPF unknown

BY DOUG BRUNK
Frontline Medical News

EXPERT ANALYSIS FROM CHEST 2016

LOS ANGELES – The optimal management of gastroesophageal reflux disease (GERD) in patients with idiopathic pulmonary fibrosis (IPF) has yet to be determined, according to Joyce S. Lee, MD.

"We need strong randomized clinical trial data to tell us whether or not medical or surgical treatment of GERD in IPF is indicated," she said at the annual meeting of the American College of Chest Physicians.

Dr. Lee, director of the interstitial lung disease program at the University of Colorado, Denver, said that GERD is nearly universal in patients with IPF, as there are multiple shared risk factors between the two conditions, including age, smoking, and male gender. "A lot of drug discovery and attention is paid to the fibroproliferative state [of IPF], but reflux is an interesting comorbidity in that it could be one of the stimuli for ongoing disease progression in IPF patients," she said. "So if reflux and treatment of reflux disease is important in patients with IPF, it could truly be a disease-modifying therapy."

Two proposed hypotheses explain the relationship between reflux and IPF. The first holds that reflux and microaspiration are involved in the pathogenesis of IPF. The second, favored by Dr. Lee, proposes that reflux and microaspiration impact the natural history, either through acute exacerbation, disease progression, or survival. Patients with IPF "have weakening of the lower esophageal sphincter, whether that's due to the presence of a hiatal hernia, medications, or just aging of the tissue there," she said. "We know how to diagnose reflux disease, but we don't know how to diagnose microaspiration, which is defined as subclinical aspiration of small droplets of gastric contents. Reflux is a risk factor for the condition of microaspiration, but it is not a perfect surrogate. Not everybody with reflux will aspirate. There is a potential role for bronchoalveolar lavage pepsin and/or bile salt as a biomarker of microaspiration, but it is not validated or standardized in IPF yet."

Reflux becomes pathologic when reflux of stomach contents causes troublesome symptoms and/or complications. "Troublesome" is defined as mild symptoms 2 or more days a week or moderate to severe symptoms more than 1 day a week. Dr. Lee said that chest physicians can diagnose GERD in their IPF patients the same way that gastroenterologists and primary care doctors do: with symptoms, barium swallow, 24-hour pH monitoring, impedance testing, and sometimes endoscopy. The 2015 IPF guidelines recommend that clinicians "use regular antacid treatment for patients with IPF (conditional recommendation, very low confidence in estimates of effect)." It does not extend to surgical treatment

Continued on following page

Inhaled antibiotic promising for bronchiectasis

BY DOUG BRUNK
Frontline Medical News

AT CHEST 2016

LOS ANGELES – Long-term inhaled ciprofloxacin therapy appears to be a safe and effective treatment option in patients with bronchiectasis, results from an international phase III trial showed.

"This is really exciting; it's the first large study of an inhaled antibiotic to show a benefit in this population," study investigator Kevin Winthrop, MD, said in an interview prior to the annual meeting of the American College of Chest Physicians. "There's a tremendous unmet need and a lot of these patients have daily struggles and their quality of life is low. To have something that would improve that would be a benefit for patients and physicians alike."

RESPIRE 1 was a global phase III trial sponsored by Bayer that enrolled adult patients with non–cystic fibrosis bronchiectasis who had at least two exacerbations in the prior 12 months and positive bacterial sputum culture for predefined bacteria. Exacerbations were defined as presence of three criteria: systemic antibiotic treatment; worsening of at least three signs and symptoms for at least 48 hours (dyspnea, wheezing, cough, 24-hour sputum volume, or sputum purulence); and fever or malaise/fatigue. A total of 416 patients in Canada, Germany, Spain, the United Kingdom, and the United States were randomized 2:1 to ciprofloxacin 32.5 mg or placebo administered twice per day using a pocket-sized inhaler as a cyclical regimen of either 14 days on/off drug or 28 days on/off drug, for 48 weeks. The primary endpoints were time to first exacerbation and frequency of exacerbation.

Compared with patients in the placebo arm, those in the ciprofloxacin dry powder for inhalation (DPI) 14-day on/off arm experienced a significantly prolonged time to first exacerbation (a mean of 336 days vs. 186 days, respectively; adjusted hazard ratio, 0.53; $P = .0005$) and a significantly reduced exacerbation frequency over 48 weeks (a mean of 0.78 vs. 1.42; adjusted incident rate of 0.61; $P = .0061$). A nonsignificant trend in favor of ciprofloxacin DPI was observed for both primary endpoints among patients in the 28-day on/off arm (time to first exacerbation: HR, 0.73; $P = .065$; frequency of exacerbations: adjusted incidence rate ratio, 0.98; $P = .89$).

Treatment-emergent adverse events and adverse events leading to discontinuation were similar across treatment groups (82% in the ciprofloxacin DPI 14-day on/off arm, 83% in the ciprofloxacin DPI 28-day on/off arm, and 83% in the pooled placebo arm. The rates of serious adverse events were also similar in the three treatment groups (17%, 20%, and 23%, respectively). "Tolerability markers like hoarseness, bronchospasm, shortness of breath, or increased cough were similar between the treatment arms," said Dr. Winthrop, who is an infectious diseases specialist at Oregon Health and Science University, Portland. "The safety profile looks really good. There were no typical fluoroquinolone types of problems such as tendinopathy reported."

Dr. Winthrop disclosed that he is a consultant for Bayer.

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Continued from previous page

with fundoplication. (Am J Resp Crit Care Med. 2015 Jul 15;192[2]: e3-19).

In an effort to measure the relationship between antacid therapy and change in forced vital capacity, Dr. Lee and her associates evaluated IPF patients from placebo arms of the three Idiopathic Pulmonary Fibrosis Clinical Research Network randomized, controlled trials. They found that, compared with patients who did not take antacid therapy at baseline, those who did experienced a slower decline in their forced vital capacity over time (Lancet Resp Med. 2013 Jul;1[5]:369-76). However, a more-recent analysis conducted by different investigators examined the placebo arms of three pirfenidone studies and found no significant effect of antacid therapy in IPF patients (Lancet Resp Med. 2016 May;4[5]:381-9). Dr. Lee said that both evaluations differed because they were secondary analyses of previously captured data. "There were also differences in the ways the trials obtained GERD history, medication indication, and dosing of the antacid therapy," she said. "There were also differences in outcomes and different populations studied."

Dr. Lee's approach to counseling IPF patients with GERD includes discussing lifestyle modifications and proton pump inhibitor (PPI) therapy – either daily or twice a day dosing. "Lifestyle modifications include weight loss, smoking cessation, raising the head of the bed 6-8 inches, and avoiding foods that cause acid reflux, including chocolate, alcohol, peppermint, and fatty or spicy foods, and avoiding large and late meals," she said. "In terms of acid suppression therapy with H_2 blockers and PPIs, symptom relief and healing of the esophagus occurs in 85%-90% of patients taking them correctly. This does not alter their risk of having microaspiration." Laparoscopic antireflux therapy (fundoplication) is indicated only after the failure of medical therapy. "The goal is to correct any hernia and tighten the lower esophageal sphincter," she said. "Efficacy and symptom relief is reported to be around 95%." She reported having no financial disclosures.

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Reflux could be a stimulus for ongoing disease progression in IPF, Dr. Lee said.

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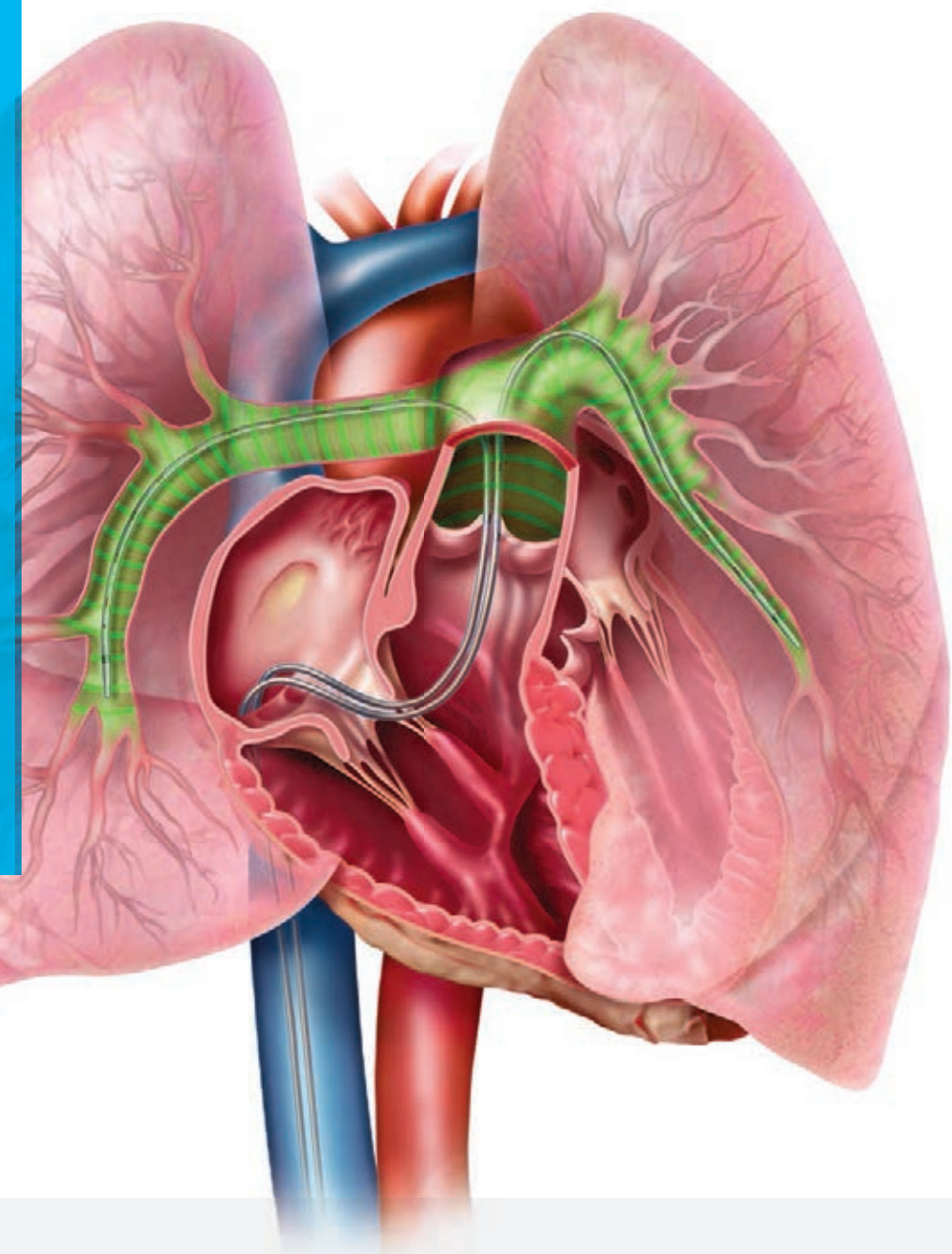

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2 *Braaten, J et al., Thromb Haemost 1997;78:1063-8; Francis, C et al. Ultrasound in Medicine and Biology 1995; 21(3):419-424; Soltani, A et al., Physics in Medicine and Biology 2008; 53:6837-6847*

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

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

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