VOL. 10 • NO. 9 • SEPTEMBER 2015

CHEST™ Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

C. S. MOTT CHILDREN'S HOSPITAL, UNIVERSITY OF MICHIGAN

Dr. Glenn E. Green, center, holds patient Garrett Peterson. At left are Garrett's parents. Dr. Richard Ohye, FCCP, wearing the lab coat, placed Garrett's splint; Scott Hollister, Ph.D., designed the splint.

3-D–printed splint for tracheobronchomalacia

BY MARK S. LESNEY
Frontline Medical News

Immediate and continued life-sustaining improvement was seen in three pediatric patients implanted with 3-D–printed tracheobronchial splints as a treatment for terminal tracheobronchomalacia (TBM), a condition of excessive collapse of the airways during respiration leading to cardiopulmonary arrest.

The particular value of such 3-D–printable biomaterials to pediatric surgery is their ability to adopt a 4-D modality – to exhibit specifically engineered shape changes in response to surrounding tissue growth over a defined time period. In addition to their malleability, these devices also are designed to be biodegradable.

These features have proven especially useful as seen in this medical device emergency use exemption study that was performed at the University of Michigan, according to a report published in Science Translational Medicine (2015 Apr 29. [doi: 10.1126/scitranslmed.3010825]).

"Our multidisciplinary

See **3-D** • *page 6*

IPF guidelines: New drugs, few established options

Conditional recommendations for some.

BY KARI OAKES
Frontline Medical News

Idiopathic pulmonary fibrosis patients and physicians have two new medication choices but fewer options among established treatments, according to updated clinical practice guidelines published by an international working group. The update of the 2011 guidelines was released by the American Thoracic Society in conjunction with the European Respiratory Society, the Japanese Respiratory Society, and the Latin American Thoracic Association.

The tyrosine kinase inhibitor nintedanib (Ofev) received a conditional recommendation for use in idiopathic pulmonary fibrosis (IPF). Pirfenidone (Esbriet), an orally administered pleiotropic antifibrotic medication, also received a conditional positive recommendation (Am J Respir Crit Care Med. 2015;192[2]:e3-19). The recommendations were formulated by a panel led by first author Dr. Ganesh Raghu, FCCP, of the University of Washington, Seattle.

Antacid therapy to reduce the microaspiration of acidic stomach contents from gastroesophageal reflux

See **IPF** • *page 4*

INSIDE

First-line combo halved PAH events

BY MARY ANN MOON
Frontline Medical News

First-line combination therapy with ambrisentan and tadalafil cut the rate of clinical events in pulmonary arterial hypertension (PAH) by half, compared with monotherapy using either drug, in an international clinical trial reported in the New England Journal of Medicine.

Ambrisentan, a selective endothelin-A-receptor antagonist, and tadalafil, a phosphodiesterase type 5 inhibitor, target different intracellular pathways known to have dysfunctional signaling in PAH, so researchers expected them to have an additive effect when combined. The study findings support the rationale of targeting multiple affected pathways early in the course of PAH, rather than following the traditional approach of sequentially adding newer agents to established background therapy, said Dr. Nazzareno Galie of the University

See **PAH** • *page 3*

CHEST Physician
151 Fairchild Ave.,
Suite 2,
Plainview, NY 11803-1709

CHANGE SERVICE REQUESTED

Presorted Standard
U.S. Postage
PAID
Permit No. 384
Lebanon Jct. KY

In pulmonary arterial hypertension (PAH)...

The power of THREE

ENDOTHELIN

NITRIC OXIDE

PROSTACYCLIN

Why don't more patients with PAH have access to these critical pathways?

There are 3 key pathways implicated in the pathogenesis of PAH: endothelin, nitric oxide, and prostacyclin pathways[1]

However, utilization of these pathways can be limited: for example, in the REVEAL Registry only 46% of patients with NYHA FC III and 59% with FC IV were on prostacyclin class therapy[1,2*]

NYHA FC=New York Heart Association functional class.

*Data from REVEAL (Registry to Evaluate Early and Long-term PAH Disease Management); US-based, observational registry involving 55 academic and community-based treatment centers. 3515 patients enrolled between March 2006 and December 2009.[3] REVEAL was funded and sponsored by Actelion Pharmaceuticals US, Inc.

References: 1. Farber HW, Miller DP, Meltzer LA, McGoon MD. Treatment of patients with pulmonary arterial hypertension at the time of death or deterioration to functional class IV: insights from the REVEAL Registry. *J Heart Lung Transplant*. 2013;32(11):1114-1122. **2.** Badesch DB, Raskob GE, Elliott CG, et al. Pulmonary arterial hypertension baseline characteristics from the REVEAL Registry. *Chest*. 2010;137(2):376-387. **3.** McGoon MD, Miller DP. REVEAL: a contemporary US pulmonary arterial hypertension registry. *Eur Respir Rev*. 2012;21(123):8-18.

ACTELION

Combination therapy excelled

PAH *from page 1*

of Bologna (Italy), and his associates.

The 4-year, industry-sponsored trial involved 500 adults treated at 120 medical centers in 14 countries for PAH with World Health Organization functional class II or III symptoms. It included patients whose disorder was idiopathic; hereditary; or associated with connective tissue disease, drugs or toxins, stable HIV infection, or repaired congenital heart defects.

The study findings support targeting multiple affected pathways early in the course of PAH.

DR. GALIE

The mean age of participants was 54 years, and 78% were women. The mean pulmonary artery pressure was 48.7 mm Hg, and mean 6-minute walk distance was 353 m at baseline.

A total of 253 patients were randomly assigned to receive oral, once-daily combination therapy, 126 to receive ambrisentan plus placebo, and 121 to receive tadalafil plus placebo.

They were assessed at monthly intervals during the 24-week treatment period and were allowed to continue therapy indefinitely.

The mean duration of use of the study medication was 517 days. Patients were followed up a final time 1 month after taking their last dose of study medication.

The primary efficacy endpoint was the first event of clinical failure, which was a composite of death, hospitalization for worsening PAH, disease progression, or unsatisfactory long-term treatment response. Only 18% of the combination-therapy group reached this endpoint, compared with 34% of the ambrisentan group, 28% of the tadalafil group, and 31% of the pooled-monotherapy group.

The hazard ratios for the primary endpoint were 0.50 for the combination therapy versus pooled monotherapy, 0.48 for combination therapy versus ambrisentan alone, and 0.53 for combination therapy versus tadalafil alone.

This treatment benefit was mainly driven by one component of the combined endpoint: The rate of hospitalization for worsening PAH was three times higher with the two monotherapies (12%) than with combination therapy (4%).

Improvement in the secondary endpoints of change in N-terminal pro–brain natriuretic peptide level, the percentage of participants with a satisfactory treatment response, and change in 6-minute walk distance all favored the combination therapy, Dr. Galie and his associates said (N Engl J Med. 2015 Aug 27. doi: 10.1056/NEJMoa1413687).

Importantly, however, "despite improvements in a variety of factors with combination therapy, we found no significant difference in WHO functional class among the study groups at week 24," they wrote.

VITALS

Key clinical point: First-line combination therapy with ambrisentan plus tadalafil cut the rate of clinical events in pulmonary arterial hypertension by half, compared with either monotherapy.

Major finding: Only 18% of the combination-therapy group reached the primary efficacy endpoint of clinical failure, compared with 34% of the ambrisentan group, 28% of the tadalafil group, and 31% of the pooled-monotherapy group.

Data source: An international, randomized, double-blind clinical trial involving 500 men and women with previously untreated PAH.

Disclosures: The AMBITION study was funded by Gilead Sciences and GlaxoSmithKline. Gilead Sciences, GlaxoSmithKline, and Eli Lilly provided the study drugs. Dr. Galie reported receiving grants and personal fees from GlaxoSmithKline, Actelion, Bayer, and Pfizer.

VIEW ON THE NEWS

Dr. Vera A. De Palo, MBA, FCCP, comments: The concept of combination therapy has been a longstanding approach of our oncology colleagues. Other medical disciplines have used the same therapeutic-combination approach, treating the target disease through different pathways with success. This trial holds promise that treatment using medications in combination offer PAH patients improved results.

IN THIS ISSUE

CHEST Physician Is Online
CHEST Physician is available on the Web at chestphysician.org

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

CHEST™ Physician
THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

CHEST Physician, the newspaper of the American College of Chest Physicians, provides cutting-edge reports from clinical meetings, FDA coverage, clinical trial results, expert commentary, and reporting on the business and politics of chest medicine. Each issue also provides material exclusive to CHEST members. Content for **CHEST Physician** is provided by Frontline Medical Communications Inc. Content for News From Chest is provided by the American College of Chest Physicians.

POSTMASTER: Send change of address (with old mailing label) to CHEST Physician, Subscription Service, 151 Fairchild Ave., Suite 2, Plainview, NY 11803-1709.
CHEST Physician (ISSN 1558-6200) is published monthly for the American College of Chest Physicians by Frontline Medical Communications Inc., 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609. Subscription price is $230.00 per year. Phone 973-206-3434, fax 973-206-9378.
Editorial Offices 5635 Fishers Lane, Suite 6100, Rockville, MD 20852, 240-221-2400, fax 240-221-2548
Advertising Offices 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609 973-206-3434, fax 973-206-9378

Scan this QR Code to visit chestnet.org/chestphysician

Frontline Medical Communications Society Partners
VP/Group Publisher; Director, FMC Society Partners Mark Branca
Editor in Chief Mary Jo M. Dales
Executive Editors Denise Fulton, Kathy Scarbeck

Creative Director Louise A. Koenig
Print Production Manager Rebecca Slebodnik
Senior Director of Classified Sales Tim LaPella, 484-921-5001, tlapella@frontlinemedcom.com
Display Advertising Managers Lauren Provenzano, 609-306-5776, lprovenzano@americanmedicalcomm.com, Michael O'Brien, 978-578-4514, mobrien@americanmedicalcomm.com
Classified Sales Representative Lauren Morgan 267-980-6087, lmorgan@americanmedicalcomm.com

FRONTLINE MEDICAL COMMUNICATIONS
Chairman Stephen Stoneburn
EVP Digital Business Development/CFO Douglas E. Grose
President/CEO Alan J. Imhoff
President, Custom Solutions JoAnn Wahl
Vice President, Finance Dennis Quirk
Executive Director, Operations Jim Chicca
Vice President, Audience Development Donna Sickles
Vice President, Custom Programs Carol Nathan
Vice President, Custom Solutions Wendy Raupers
Vice President, Marketing & Customer Advocacy Jim McDonough
Vice President, Sales Phil Soufleris
Vice President, Society Partners Mark Branca
Corporate Director, Research & Communications Lori Raskin
Director, eBusiness Development Lee Schweizer
In affiliation with Global Academy for Medical Education, LLC
Vice President, Medical Education & Conferences Sylvia H. Reitman, MBA
Vice President, Events David J. Small, MBA

Timely epinephrine for pediatric cardiac arrest

BY MARY ANN MOON
Frontline Medical News

Delay in administering epinephrine is associated with significantly poorer outcomes among pediatric patients who have in-hospital cardiac arrest with an nonshockable rhythm, according to a report published online Aug. 25 in JAMA.

For the approximately 16,000 U.S. children and adolescents in this patient population each year, epinephrine is the recommended first-line pharmacologic therapy, even though no randomized placebo-controlled trials have ever been performed to support this practice.

©JUPITERIMAGES/THINKSTOCKPHOTOS.COM

It is highly unlikely that any such study will ever be done, given the ethical considerations, so to examine the effect of the timing of epinephrine therapy, investigators analyzed data from the Get With the Guidelines-Resuscitation registry concerning 1,558 patients aged 0-18 years who were treated during a 15-year period, said Dr. Lars W. Andersen of the department of emergency medicine at Beth Israel Deaconess Medical Center, Boston, and the department of anesthesiology at Aarhus (Denmark) University and his associates.

All the patients received chest compressions and at least one epinephrine bolus while pulseless with a documented nonshockable initial rhythm. The median age was 9 months, and the median time to first epinephrine dose was 1 minute (range, 0-20 minutes). A total of 37% of these patients received their first dose of epinephrine within 1 minute after loss of pulse was noted, and 15% received their first dose more than 5 minutes afterward.

Delay in epinephrine treatment was significantly associated with a lower chance of survival to hospital discharge (relative risk, 0.95 per minute of delay), the primary outcome measure of the study. In addition, longer time to epinephrine delivery was significantly associated with a decreased chance of return to spontaneous circulation (RR, 0.97 per minute of delay), for survival at 24 hours (RR, 0.97 per minute of delay), and for survival with favorable neurologic outcome (RR, 0.95 per minute of delay).

In a further analysis of the data, patients were divided into two groups according to the length of time before epinephrine administration. The 1,325 patients who received epinephrine within 5 minutes had a 33.1% rate of survival to hospital discharge, while the 233 who received epinephrine after 5 minutes had elapsed had a significantly lower 21.0% rate of survival to hospital discharge, Dr. Andersen and his associates said (JAMA. 2015 Aug 25. doi: 10.1001/jama.2015.9678).

The findings of the observational study cannot confirm that treatment delay causes poorer outcomes. Time to epinephrine administration may be a marker of other aspects of resuscitation.

VIEW ON THE NEWS

Guidelines upheld

The findings provide fairly strong evidence that following current guidelines for epinephrine timing is best practice, supporting an American Heat Association class I strength of recommendation.

The investigators are correct to note that observational data cannot establish causality. Almost all of these cardiac arrests were witnessed; approximately two-thirds occurred in the pediatric intensive care unit, operating room, or postanesthesia setting; and half of the patients were receiving mechanical ventilation. So it is possible that the link between timing of epinephrine and outcomes may simply reflect factors such as the circumstances of the cardiac arrest, the presence of an airway and intravenous access, or the quality of chest compressions.

Dr. Robert C. Tasker and Dr. Adriennne G. Randolph are with the division of critical care medicine, department of anesthesia, perioperative, and pain medicine at Boston Children's Hospital and the department of anesthesia at Harvard Medical School. Dr. Tasker is also with the department of neurology at both institutions and Dr. Randolph is also with the department of pediatrics at Harvard. Both authors reported having no relevant financial conflicts of interest. Dr. Tasker and Dr. Randolph made these remarks in an accompanying editorial (JAMA. 2015;314:776-7. doi: 10.1001/jama.2015.9527).

Guidelines find little evidence

IPF *from page 1*

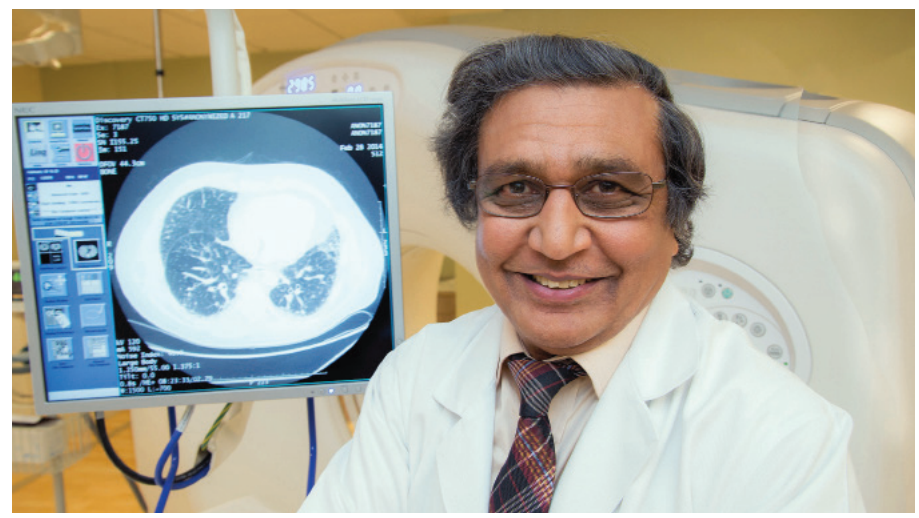
received a conditional positive recommendation. Abnormal gastroesophageal reflux occurs in up to 90% of IPF patients, according to Dr. Raghu and his coauthors.

No other treatments show efficacy when rigorously examined, Dr. Raghu said. "We haven't shown that any treatment regimen affects how patients feel or function. We haven't improved survivability or quality of life."

The guideline authors issued a strong recommendation against use of prednisone, azathioprine, and *N*-acetylcysteine as triple therapy, noting "a clear negative effect… for multiple patient–important outcomes" in a trial that was stopped early for harm. They recommended revisiting the diagnosis in instances where IPF patients seem to be receiving benefit from triple therapy.

N-acetylcysteine as monotherapy for IPF showed no improvement in mortality, lung function studies, or quality of life in three studies, although two studies showed improvement on the 6-minute walk test. The authors thus issued a conditional recommendation against using *N*-acetylcysteine as monotherapy.

The 2015 clinical practice guidelines also strengthened the recommendation against using warfarin for anticoagulation to treat IPF; warfarin had received a conditional recommendation against treatment in the previous guidelines released in 2011. Although studies provide "biological plausibility for a mechanistic link between thrombosis and lung fibrosis," Dr. Raghu and his coauthors noted increased mortality and no improvement in lung function in some studies comparing warfarin with placebo. However, warfarin should still be used as clinically indicated in patients with other indications for its use as an anticoagulant.



CLARE MCLEAN/UNIVERSITY OF WASHINGTON MEDICINE

Dr. Ganesh Raghu: "We haven't shown that any treatment regimen affects how patients feel or function. We haven't improved survivability or quality of life."

Endothelin receptors (ERs) can promote epithelial to mesenchymal transition via cytokine mediators, a process associated with organ fibrosis. Thus, ER antagonists have been studied to treat IPF. Ambrisentan (Letairis) is a selective ER type-A antagonist that, in a single, randomized, controlled trial, was associated with worsening respiratory function and increased mortality. The guidelines thus strongly recommend against the use of ambrisentan for IPF.

The dual-acting ER antagonists bosentan (Tracleer) and macitentan (Opsumit) target both ER-A and ER-B sites. Dr. Raghu and his coauthors pooled results of three studies examining one or the other of the two dual-acting ER antagonists, find-

Continued on following page

Continued from previous page

ing no overall effect on mortality but a small improvement in the composite outcome of death or disease; they issued a conditional recommendation against using either bosentan or macitentan.

For IPF patients with pulmonary hypertension (PH), "the committee felt that patients with PH secondary to IPF might benefit … however, the evidence did not allow a specific subgroup recommendation."

Sildenafil (Revatio) is a phosphodiesterase-5 inhibitor that has been used in patients with PH and right ventricular dysfunction; however, in the limited data available for its use in patients with IPF, no benefit on mortality, dyspnea, or IPF exacerbations was seen. There was a slight benefit on quality of life, but sildenafil got a qualified negative recommendation. No subgroup recommendations were made for patients with PH and/or right ventricular dysfunction.

Finally, Dr. Raghu and his coauthors did not make a recommendation regarding single, compared with bilateral, lung transplantation for individuals with moderate or severe IPF. "The decision to give bilateral lung transplantation to a single patient rather than give single-lung transplantation to two patients, including the effect on health inequity, must be considered," they said, calling for randomized, controlled trials.

The authors of the guidelines followed a strict protocol to recuse themselves from deliberation when conflicts existed. Conflicts of interest and a detailed protocol description are in the full text of the guidelines.

koakes@frontlinemedcom.com
On Twitter @karioakes

VIEW ON THE NEWS

IPF guidelines set framework to move forward

The new IPF guidelines set a critical framework for where we are and where we need to push forward.

As we move toward more and better treatments, we should

be aware that care of IPF patients should be multifaceted, and not just pharmacologic. In order to address the suffering associated with this disease, we need to use all available modalities: supplemental oxygen; physical therapy; and psychological support. Lung fibrosis is a heterogeneous disease, and by focusing on how individual patients are affected, we can help meet their needs. The fund of available knowledge has been addressed in an evidence-based fashion. Unfortunately, this is the state of affairs; however, now we can begin to answer the questions that need to be answered.

Dr. Gregory P. Cosgrove, FCCP, is the chief medical officer of the Pulmonary Fibrosis Foundation and holds the endowed chair of interstitial lung disease at National Jewish Health in Denver. His comments are summarized from an interview.

Splint prevents airway collapse

3-D *from page 1*

team designed an archetype device to allow radial expansion of the affected airway over the critical growth period while resisting external compression and intrinsic collapse," wrote Dr. Robert J. Morrison, FCCP, and Dr. Glenn E. Green, of the University of Michigan, Ann Arbor, and their colleagues.

The study population involved three infant boys, aged 3 months, 5 months, and 16 months at time of treatment. In each patient, a sternotomy exposed their affected airways.

The 3-D–printed splint, consisting of conjoined rib-like C-shaped arches, was placed around the affected airway and secured with polypropylene sutures.

The splint counters external pressure on the airway and holds it open. Because the splint is malleable, with an expandable opening placed opposite to the main collapsing pressure, it is capable of expanding as the airway grows.

Examination of the airway imme-

VITALS

Key clinical point: The use of 3-D–printed airway implants mitigated life-threatening tracheobronchomalacia (TBM) in three infants.

Major finding: Three infants with a terminal form of TBM ceased exhibiting life-threatening airway disease and showed continued growth of pulmonary airways after 3-D tracheal implants.

Data source: A study performed at the University of Michigan, Ann Arbor, of three infants with terminal TBM who received a medical device emergency use exemption for a 3-D tracheal implant.

Disclosures: The study was funded by the National Institutes of Health. Two of the study authors were coinventors of the device for which they have filed a patent. There were no other disclosures.

diately after placement demonstrated patency, which was confirmed 1 month later.

Results showed the benefit of the splints for all three patients, although total results were complicated by additional comorbidities:

• **Patient 1** – Blood gases returned

Continued on following page

Continued from previous page

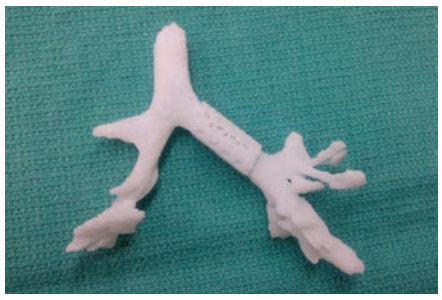
to normal immediately after implantation and remained normal at 3 months' follow-up. A week after implantation, weaning from mechanical ventilation was initiated and, 3 weeks after the procedure, the child was discharged to home.

'We report successful implantation of patient-specific bioresorbable airway splints for the treatment of severe TBM. The personalized splints conformed to the patients' individual geometries and expanded with airway growth (in the 'fourth dimension').'

Repeat imaging at 1, 3, 6, 12, and 39 months postoperatively demonstrated continued resolution of the TBM, with evidence of fragmentation and degradation of the splint at 39 months.

• **Patient** – Immediately after implantation of the device, blood gases improved greatly and the left lung perfused. The patient had opioid and benzodiazepine dependence from long-term ventilator support, requiring a longer controlled wean from the ventilator.

Four weeks after surgery, the



C.S. Mott Children's Hospital, University of Michigan

The 3-D–printed model of Garrett Peterson's trachea with 3D printed splints attached.

patient was transitioned to a portable ventilator system, completely weaned at 15 weeks, and discharged from the hospital to home for the first time in his life.

• **Patient 3** – After implantation, the patient ceased experiencing life-threatening desaturation episodes and showed sustained improvement in blood gases. Imaging showed continued patency of the left main bronchus with resolution of left-lung air trapping.

However, at 14 months post implantation, the patient remained on permanent ventilator support, "presumably because of distal left segmental bronchomalacia beyond what the splint was designed to address," according to Dr. Morrison and his colleagues.

"We report successful implantation of patient-specific bioresorbable airway splints for the treatment of severe TBM. The personalized splints conformed to the patients' individual geometries and expanded with airway growth (in the 'fourth dimension')," they stated.

"The three pediatric patients implanted with these 3-D–printed airway splints had a terminal form of TBM. The clinical improvement in each case was immediate and sustained, suggesting that improvement is not attributable to the natural history of the disease alone," they added.

In summarizing the future of the technology, they pointed out a list of problems: The regulatory framework for a customizable device intended for rare diseases is daunting; inadequate animal models of human growth exist; further work was needed to characterize 3-D–printed biomaterials and the effect of the printing process on final device performance; and industry guidance was lacking on validating materials, manufacturing techniques, sterilization, and performance of 3-D–printed devices.

mlesney@frontlinemedcom.com

VIEW ON THE NEWS

Dr. Susan Millard, FCCP, comments: The 3-D–printer applications for tracheobronchomalacia requiring mechanical ventilation are an awesome discovery for pediatric pulmonary patients, families, and their treating physicians! The prognosis for these infants and toddlers has been poor if routine mechanical ventilation was not able to support the patients and allow them to grow. This technology offers hope where there had previously been no hope! We look forward to more research that will allow for establishing clear-cut guidelines regarding which patients would most benefit from this surgical intervention.

Lung cancer biomarker moves into the clinic

BY SUSAN LONDON
Frontline Medical News

SEATTLE – A new biomarker for bronchial epithelium that helps identify smokers with suspicious lesions who have lung cancer is now ready for clinical use. And one for nasal epithelium that could be used for screening may not be far behind.

"There is clearly a critical unmet need to develop molecular biomarkers to address some of the challenges that we now face since we have instituted CT screening for lung cancer," Dr. Avi Spira said at a joint meeting of the Global Biomarkers Consortium and World Cutaneous Malignancies Congress.

Although the National Lung Screening Trial established that annual chest CT among high-risk current and former smokers reduces their risk of death from lung cancer (N Engl J Med. 2011;365:395-409), a vast majority of those who screen positive do not have lung cancer. Also, screening only patients who meet criteria set by the trial will pick up less than half of all lung cancers in the United States.

"That leads to two critical unmet needs for molecular biomarkers in the so-called post–National Lung Screening Trial era," said Dr. Spira, professor of medicine, pathology and laboratory medicine, and bioinformatics; chief of the division of computational biomedicine; and director of the translational bioinformatics program, Clinical and Translational Science Institute, all at Boston University.

"The first is … we desperately need molecular biomarkers that can distinguish a benign nodule found on CT versus a malignant one," he said. "The second and arguably longer-term biomarker that we need is to distinguish which smokers would benefit from CT screening annually."

Much of his team's research in this area builds on the concept of field of injury. "The idea here is if you smoke, even though lung cancer tends to develop deep within the parenchyma of your lung, all of the epithelial cells that line your respiratory tract have genomic alterations that reflect the presence of that cancer," Dr. Spira explained. Thus, profiling epithelial cells anywhere in the airway could be used for early detection and risk assessment.

He and his colleagues developed a 23-gene signature for use on bronchial epithelial cells. The biomarker was validated in the Airway Epithelium Gene Expression in the Diagnosis of Lung Cancer (AEGIS) 1 and 2 trials among 639 current and former smokers undergoing bronchoscopy for suspicious nodules seen on CT.

'The negative predictive value, which is really what drives the clinical utility of this test, is above 90%.'

DR. SPIRA

With 1 year of follow-up, biomarker sensitivity was 88%-89%, while specificity was 47% (N Engl J Med. 2015;373:243-251). "However the negative predictive value, which is really what drives the clinical utility of this test, is above 90%. And that's what we believe will drive physicians to use the test – [determining] who can they avoid sending for an unnecessary [biopsy] procedure," Dr. Spira said. Bronchoscopy alone had sensitivity of about 75%, but bronchoscopy combined with the gene signature had sensitivity of 97%.

Subgroup analyses showed the biomarker had superior sensitivity for detecting lung cancer when lesions measured no more than 3 cm or were located in the lung periphery, and when patients had early-stage disease. It performed similarly well across different types of tumors.

Of note, among patients whose pretest probability of cancer fell in the intermediate range (10%-60%), bronchoscopy had an 83% nondiagnostic rate, but the biomarker had 88% sensitivity and a 91% negative predictive value. "That means if you have a nondiagnostic bronchoscopy in a patient who is at intermediate pretest risk for disease, a negative gene expression test would mean there is a less than 10% chance this is cancer. That's where a physician might feel, okay, I don't have to go on and do a biopsy, I can watch that patient serially with CT scans of the chest," Dr. Spira said.

The biomarker test is now clinically available (Percepta, manufactured by Veracyte). "It's the first of what I believe are many molecular biomarkers that are going to be emerging in the clinical space for the early detection of lung cancer," he said.

"The multimillion dollar question is why are we seeing gene expression changes in normal-appearing cells so far away from where the tumor arises? We don't have the full answer to that yet, but based on the genes that are changing, we have developed some hypotheses," Dr. Spira said.

Some of the down-regulated genes are involved in antioxidant and DNA repair pathways, suggesting that the smokers who ultimately get cancer have less of a protective response to smoking. And some of the up-regulated genes include ones in the PI3 kinase signaling pathway.

"What we are seeing in the proximal airway isn't necessarily reflecting the presence of the cancer but the susceptibility, and that's a really important distinguishing factor because then perhaps the test could be used as a screening tool," Dr. Spira said.

As not all smokers at elevated risk for lung cancer will undergo bronchoscopy, one of the researchers' future goals is to move biomarker testing to a less invasive site. They are focusing on the nose, using nasal epithelium collected by brushings from the inferior turbinate.

An analysis of nasal epithelium collected at the time of bronchoscopy in the AEGIS trials has shown that a 200-gene signature performs well for distinguishing between patients with and without lung cancer, Dr. Spira reported. Furthermore, the changes in gene expression profile in the nose were similar to those seen in the bronchus.

Such a biomarker might have best clinical utility in two other settings, he proposed. The first would be in patients having nodules that are clearly not accessible by bronchoscopy, in which case the biomarker would be applied for diagnosis. The second would be in smokers being seen for routine annual exams, in which case it would be used to identify those who should have CT surveillance.

"We are hopeful that the nasal epithelium can serve as a less invasive surrogate for the bronchus and ultimately allow us to move airway profiling into the screening setting for lung cancer," he said.

Dr. Spira disclosed that he receives intellectual property rights and consulting fees from, and has an ownership interest in, Veracyte.

Limited resection inferior for elderly with early NSCLC

BY MARY ANN MOON
Frontline Medical News

Limited resection is inferior to lobectomy for older patients with early-stage invasive non-small cell lung cancer, yielding lower overall survival and cancer-specific survival, according to a study published in the Journal of Clinical Oncology.

Limited resection – wedge resection or segmentectomy – is increasingly chosen over lobectomy for patients older than 65 because it is thought to yield equivalent survival among patients who are already near the end of their lives and to cut down on perioperative and postoperative complications. Moreover, the number of these surgeries is expected to increase substantially when the recently released U.S. Preventive Services Task Force recommendations for lung cancer screening are fully implemented, said Dr. Rajwanth R. Veluswamy of the division of hematology and medical oncology, Mount Sinai University, New York, and his associates.

However, the evidence supporting the equivalency of limited resection to lobectomy is scant and not of high quality. To examine the issue more closely, the investigators analyzed survival outcomes for 3,147 patients aged 65 and older who were included in the nationally representative population-based Surveillance, Epidemiology, and End Results (SEER) database. These patients had stage 1A NSCLC of 2 cm or less in diameter and were treated surgically in 1998 through 2009.

Limited resection was found to be inferior to lobectomy regarding overall survival (hazard ratio, 1.21) and lung cancer–specific survival (HR, 1.66) among patients with invasive adenocarcinoma. Limited resection also was inferior to lobectomy regarding overall survival (HR, 1.21) and lung cancer–specific survival (HR, 1.41) among patients with squamous cell carcinoma, Dr. Veluswamy and his associates said (J Clin Oncol. 2015 Aug. 3. doi:10.1200/JCO.2014.60.6624).

"Our findings should help decide the best treatment for older patients by balancing the potential short- and long-term risks of limited resection versus lobectomy," they said.

The investigators added that they focused on patients older than age 65

Continued on page 13

Considering treatment options for your pulmonary arterial hypertension (PAH) patients?

REVATIO® (sildenafil)— is now available as an oral suspension treatment for PAH

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.

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.

Consider REVATIO oral suspension for your appropriate PAH patients.
To learn more about REVATIOHCP.com.

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

Revatio® sildenafil
20 mg tablets

RVU751722-02

June 2015

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

Continued from page 10

because that is the age group most frequently affected by invasive NSCLC and most likely to be considered for limited resection. These results cannot be extrapolated to younger patients because they have longer life expectancies and thus higher risk of recurrence after "limited" treatment.

The U.S. Agency for Healthcare Research and Quality supported the study. Dr. Veluswamy had no disclosures; his colleagues reported associations with Pfizer, Otsuka, Teva Neuroscience, EHE International, United BioSource, Ethicon, Covidien, Genentech, IMS Health, Merck, Bristol-Myers Squibb, Quintiles, and Sanofi.

Solid histology bodes poor survival in adenocarcinoma

BY KARI OAKES
Frontline Medical News

For patients with lung adenocarcinoma, a predominantly solid tumor subtype was associated with earlier recurrence and shorter post-recurrence survival (PRS). These patients were more likely to have more extrathoracic and multisite recurrences, according to a single-center retrospective record review of stage I lung adenocarcinoma patients who received surgical resection.

"Despite curative-intent surgical resection, tumor recurrence and spread remain the primary causes of cancer-related death among patients with early-stage lung cancer," wrote Dr. Hideki Ujiie of Memorial Sloan Kettering Cancer Center, New York (J Clin Oncol. 2015 Aug 10. doi:10.1200/JCO2015.60.9818).

To identify which tumor subtypes place patients at higher risk for recurrence, Dr. Ujiie and his colleagues reviewed records of 1,120 patients undergoing complete surgical resection for stage I lung adenocarcinoma from 1999 to 2009 at the cancer center.

The 2-year PRS in the patients studied was 45%, with median PRS of just over 26 months; median follow-up was 60 months. On multivariable analysis, the researchers found that predominantly solid tumor type was the variable most strongly associated with worse PRS (Hazard Ratio 1.76; 95% Confidence Interval 1.11-2.77; $P = .016$).

"The risk of recurrence for tumors with solid predominant histologic subtype peaked within 12 months and ... these tumors were associated with a higher incidence of extrathoracic, multiple-site recurrences in patients with stage I lung adenocarcinoma," the researchers said.

The study was prompted, in part, by the new International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society lung cancer classification system, which recognizes the histologic heterogeneity of lung adenocarcinoma subtypes. Dr. Ujiie and his coauthors sought to use these characterizations to develop prognostic factors for recurrence risk and PRS. Their findings have clinical implications: "[R]egular surveillance is even more important when tumors of aggressive predominant subtypes (e.g., solid predominant histologic pattern) are present," they wrote.

The National Institutes of Health and the U.S. Department of Defense funded the study. Dr. Ujiie had no disclosures. Several coauthors reported ties to pharmaceutical companies.

koakes@frontlinemedcom.com
On Twitter @karioakes

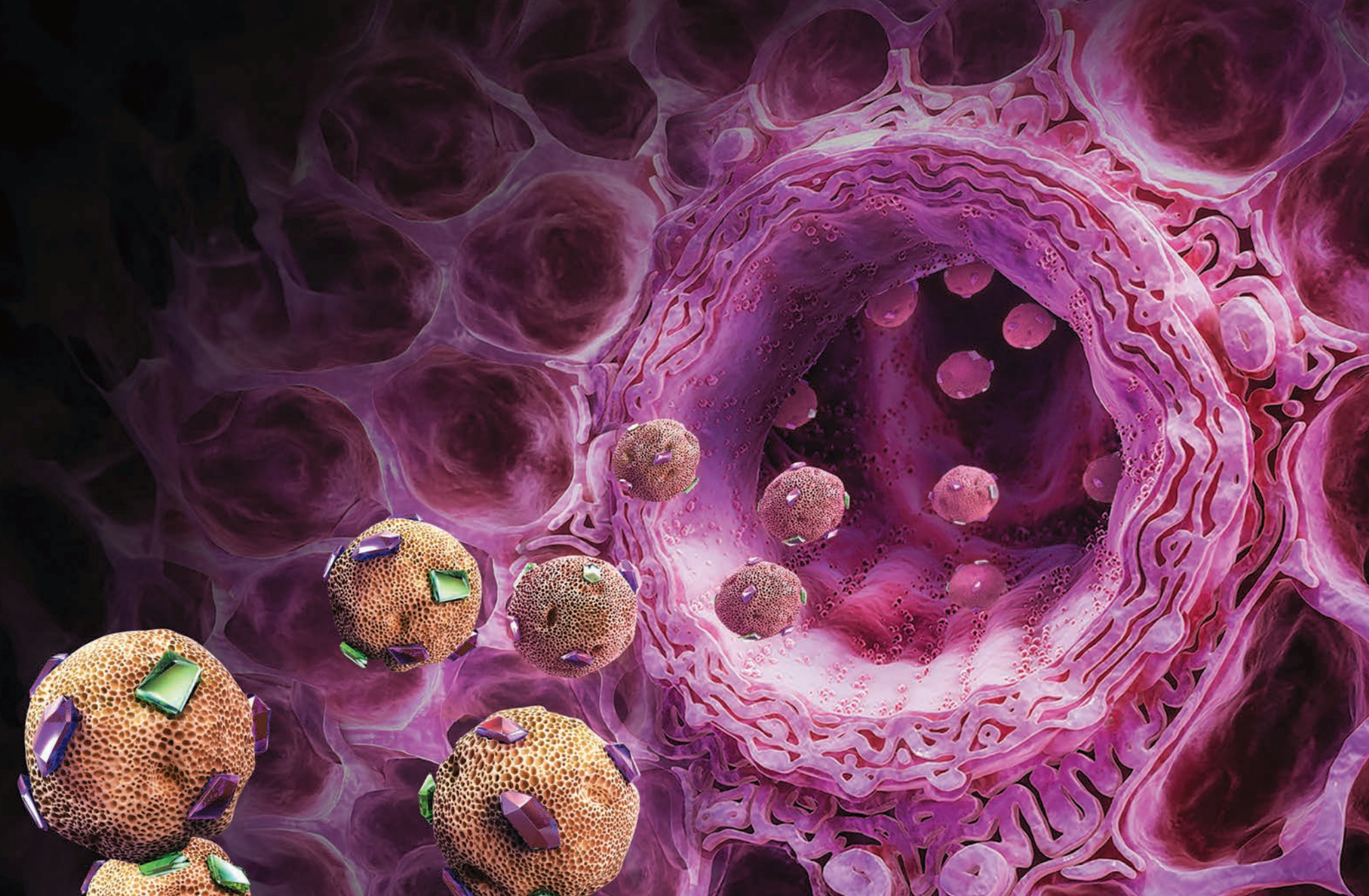
INTRODUCING

CO-SUSPENSION TECHNOLOGY

THE NEW SCIENCE OF INTELLIGENT DELIVERY IN RESPIRATORY MEDICINE

Exploring a new formulation for inhaled drug delivery

A specially engineered, phospholipid carrier particle with multiple drug crystals[1]



Visit Co-SuspensionParticles.com to Learn More

CO-SUSPENSION TECHNOLOGY

All images are for illustrative purposes only.

Reference: 1. Vehring R, Lechuga-Ballesteros D, Joshi V, Noga B, Dwivedi SK. Cosuspensions of microcrystals and engineered microparticles for uniform and efficient delivery of respiratory therapeutics from pressurized metered dose inhalers. *Langmuir*. 2012;28(42):15015-15023.

AstraZeneca

CT pegs COPD patients at high risk for exacerbations

BY SHANNON AYMES
Frontline Medical News

Chronic obstructive pulmonary disease patients who have emphysema and airway thickening on computed tomography have more hospitalizations and more severe dyspnea, according to Dr. Van Tho Nguyen and colleagues at Shiga (Japan) University of Medical Science, and the University Medical Center at Ho Chi Minh City, Vietnam.

Pulmonary function testing may not fully represent the heterogenous characteristics of COPD, said the researchers, who used quantitative CT to develop a method to phenotype COPD and examine differences in clinical outcomes between mixed phenotype patients and those with emphysema- and airway-dominant phenotypes.

The mixed phenotype was linked with more severe dyspnea and more frequent hospitalizations, and these patients may need more attention and interventions, the researchers said (Ann Am Thorac Soc. 2015;12[7]988-96).

The researchers did pulmonary function testing and whole-lung CT scans on 240 male smokers with COPD and 187 without COPD. Four phenotypical classifications were defined on the basis of measurements of airway thickening and percentage of low-attenuation volume (threshold of -950 Hounsfield units) – CT-normal, airway-dominant, emphysema-dominant, and mixed phenotype.

Of the 240 men with COPD, 43% had the emphysema-dominant phenotype, 22% had the CT-normal phenotype, 19% had a mixed phenotype, and 16% had the airway-dominant phenotype.

Patients with mixed phenotype COPD had more severe air trapping (residual volume/total lung capacity, RV/TLC) and airflow limitation (FEV_1/FVC and FEV_1% predicted) compared with the other phenotypes.

Mixed phenotype COPD patients had lower percent predicted carbon monoxide diffusing capacity than the airway-dominant phenotype (*P* less than .0001) and the CT-normal phenotype (*P* less than .0001).

Patients with mixed phenotype COPD had 2.0-3.6 more hospitalizations for COPD exacerbations (*P* less than .05) and more severe dyspnea (*P* less than .01) than did the other CT-based COPD phenotypes.

The differences persisted after adjustment for body mass index (BMI), FEV_1, age, smoking status, and pack-years.

The mixed COPD phenotype was linked with a longer duration of disease and a higher blood neutrophil count, which has been linked to higher risk of recurrent exacerbations and may lead to emphysema progression.

These patients have more severe dyspnea and therefore are diagnosed earlier or it may take longer for both airway thickening and emphysema to develop, the researchers noted.

Two coauthors disclosed ties to the Japan Society for the Promotion of Science, GlaxoSmithKline, and Nippon Boehringer Ingelheim.

VIEW ON THE NEWS

Dr. Vera A. De Palo, MBA, FCCP comments: The authors of this study visually demonstrate the heterogeneous nature of COPD. They link the image findings with COPD phenotype and health care utilization. This knowledge may help focus attention on those patients at risk for readmission and on the search for strategies of symptom relief and better lung health.

Metformin did not cut COPD exacerbation rate

DOUG BRUNK/FRONTLINE MEDICAL NEWS

"Metformin works through reducing hepatic glucose output and increasing insulin sensitivity – and the effect may take several months," said Dr. Emma H. Baker.

BY DOUG BRUNK
Frontline Medical News

DENVER – Among patients hospitalized for chronic obstructive pulmonary disease (COPD) exacerbations, acute administration of metformin had no detectable impact on clinical recovery, based on results from a single-center study.

Patients hospitalized for COPD exacerbations are more likely to have longer hospital stays and to experience adverse outcomes if their blood glucose levels are elevated, Emma H. Baker, Ph.D., said in an interview at an international conference of the American Thoracic Society.

"The aim of the current study was to see if lowering blood glucose in COPD patients would reduce adverse outcomes," said Dr. Baker, professor of clinical pharmacology at the Institute for Infection and Immunity at St. George's University of London. A previous study suggested that tight glycemic control with insulin improved outcomes among COPD patients in the ICU; however, a large, randomized, multicenter trial showed no difference in outcomes and a risk for hypoglycemia. The researchers wanted to see whether metformin would prove a safer option.

Dr. Baker and her associates randomized 51 patients in a 2:1 fashion to receive metformin or placebo. The metformin dose was escalated to 2 g/day over 4 days and continued for 1 month. Outcome measures included the Exacerbations of Chronic Pulmonary Disease Tool (EXACT), the COPD Assessment Test (CAT), and the rates of recurrent health care use events such as antibiotic or steroid prescription and hospital readmission. Of the 51 patients, 34 received metformin and 18 received placebo. The mean age was 67 years; 39% were women.

Compared with baseline, the EXACT scores improved by 4.2 points at day 5, 5-7 points at day 10, and 6.3 points at day 28 (*P* less than .05 for all). However, the researchers observed no significance differences between the metformin and placebo groups in terms of improvements on EXACT scores. Similarly, CAT scores improved by a mean of 4.2 points over the course of the study, largely between baseline and hospital discharge. There were no significant differences between the metformin and placebo groups at any time point. The median time to a recurrent health care use event was similar between the groups (46 days in the metformin group, compared with 40 days in the placebo group; $P = .682$).

"Metformin works through reducing hepatic glucose output and increasing insulin sensitivity – and the effect may take several months," Dr. Baker said. "What we did show is that metformin seems to be safe in COPD patients," with no evidence of lactic acidosis.

Diabetes and hyperglycemia are common in COPD, and were associated with more frequent COPD exacerbations and worse outcomes from exacerbations, Dr. Baker noted.

The study was sponsored by the Medical Research Council of the United Kingdom and the British Lung Foundation funded the study. Dr. Baker had no disclosures.

dbrunk@frontlinemedcom.com
On Twitter @dougbrunk

In refractory asthma, think vocal cord dysfunction

BY BRUCE JANCIN
Frontline Medical News

ESTES PARK, COLO. – Consider the possibility of comorbid vocal cord dysfunction in patients with asthma that doesn't respond to aggressive therapy.

"Vocal cord dysfunction is an important diagnosis. It's something to think about in your toughest-to-treat asthma patients. I think you'll see a lot of it," Dr. Robert L. Keith, FCCP, predicted at a conference on internal medicine sponsored by the University of Colorado.

Vocal cord dysfunction (VCD) is defined as adduction or closure of the vocal cords on inspiration or exhalation. VCD is a notorious mimicker of asthma. The two conditions

©BANANASTOCK/THINKSTOCKPHOTOS.COM

share many signs and symptoms, including wheezing, shortness of breath, cough, chest tightness, stridor, and throat tightness, noted Dr. Keith, professor of medicine in the department of pulmonology and critical care medicine at the university.

In a classic study, investigators at National Jewish Health in Denver found that among patients referred to the tertiary center for asthma who had failed to respond to conventional therapies, 30% turned out to have asthma plus VCD and another 10% actually had VCD alone (Semin Respir Crit Care Med. 1994;15[2]:161-67).

The diagnosis of VCD is suggested by worsening symptoms upon bronchoprovocation during pulmonary function testing, with no change in forced expiratory volume in 1 second (FEV_1) or PC20, which is the dose of the provocative inhalational agent required to produce a 20% drop in FEV_1.

"You can think of VCD as extrathoracic obstruction," Dr. Keith said.

Definitive diagnosis of VCD is made by direct fiber optic laryngoscopy carried out with no sedation, which would affect the vocal cords. Look for abnormal vocal cord movements during a variety of patient maneuvers, including panting and full inhalation and exhalation, Dr. Keith advised.

The cornerstone of VCD treatment is specific breathing exercises which were pioneered by and are still typically led by speech therapists. Hypnosis, biofeedback, and psychotherapy can be helpful. Patients experiencing a severe acute attack obtain benefit from inhaling a helium/oxygen mixture.

Injection of botulinum toxin or sectioning of the laryngeal nerve in order to affect vocal cord movement are other options, although Dr. Keith said he has never found it necessary to refer patients with VCD for those therapies.

bjancin@frontlinemedcom.com

Reduce lung function decline

Delay IPF progression with Esbriet

Indication

Esbriet® (pirfenidone) is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

Select Important Safety Information

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

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.

Esbriet®
(pirfenidone) capsules 267 mg

Proven to delay progression in IPF[1]

- Fewer patients had a meaningful decline in lung function with Esbriet at 52 weeks vs placebo (17% vs 32% of patients had ≥10% decline in %FVC, $P<0.001$). Treatment effect was evident at 13 weeks ($P<0.001$) and increased through trial duration[1,2,*,†]
- More patients had stable lung function with Esbriet than with placebo at 52 weeks (23% vs 10%)[2,*,‡]
- In clinical trials, elevated liver enzymes, photosensitivity reactions, and gastrointestinal disorders have been reported with Esbriet[2]
- Esbriet has been approved outside the US since 2011, with approximately 15,000 patients treated with pirfenidone worldwide[3]

Learn more about Esbriet and how to access medication at Esbriet.com.

*The efficacy of Esbriet was evaluated in three phase 3, randomized, double-blind, placebo-controlled 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 $\%DL_{CO}$ between 30%-90%. The primary endpoint was change in %FVC from baseline to week 52.

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

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

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

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

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

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

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at 1-888-835-2555.

Please see Brief Summary of Prescribing Information on adjacent pages for additional important safety information.

†Rank ANCOVA with lowest rank imputation for missing data due to death. Patients who died were counted in the ≥10% decline category.
‡Stable was defined as no decline in lung function.

References: 1. King TE Jr, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med.* 2014;370:2083-2092. Erratum in: *N Engl J Med.* 2014;371:1172. **2.** Esbriet full Prescribing Information. InterMune, Inc. October 2014. **3.** InterMune, Inc. Data on file.

Genentech
A Member of the Roche Group

Esbriet®
(pirfenidone) capsules 267 mg

Rx only

BRIEF SUMMARY

The following is a brief summary of the full Prescribing Information for ESBRIET® (pirfenidone). Please review the full Prescribing Information prior to prescribing ESBRIET.

INDICATIONS AND USAGE

ESBRIET is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Elevated Liver Enzymes

Increases in ALT and AST >3 × ULN have been reported in patients treated with ESBRIET. Rarely these have been associated with concomitant elevations in bilirubin. Patients treated with ESBRIET 2403 mg/day in the three Phase 3 trials had a higher incidence of elevations in ALT or AST ≥3 × ULN than placebo patients (3.7% vs. 0.8%, respectively). Elevations ≥10 × ULN in ALT or AST occurred in 0.3% of patients in the ESBRIET 2403 mg/day group and in 0.2% of patients in the placebo group. Increases in ALT and AST ≥3 × ULN were reversible with dose modification or treatment discontinuation. No cases of liver transplant or death due to liver failure that were related to ESBRIET have been reported. However, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury, that could lead to death or the need for liver transplants in some patients. Conduct liver function tests (ALT, AST, and bilirubin) prior to the initiation of therapy with ESBRIET in all patients, then monthly for the first 6 months and every 3 months thereafter. Dosage modifications or interruption may be necessary for liver enzyme elevations *[see Dosage and Administration sections 2.1 and 2.3 in full Prescribing Information]*.

Photosensitivity Reaction or Rash

Patients treated with ESBRIET 2403 mg/day in the three Phase 3 studies had a higher incidence of photosensitivity reactions (9%) compared with patients treated with placebo (1%). The majority of the photosensitivity reactions occurred during the initial 6 months. Instruct patients to avoid or minimize exposure to sunlight (including sunlamps), to use a sunblock (SPF 50 or higher), and to wear clothing that protects against sun exposure. Additionally, instruct patients to avoid concomitant medications known to cause photosensitivity. Dosage reduction or discontinuation may be necessary in some cases of photosensitivity reaction or rash *[see Dosage and Administration section 2.3 in full Prescribing Information]*.

Gastrointestinal Disorders

In the clinical studies, gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastro-esophageal reflux disease, and abdominal pain were more frequently reported by patients in the ESBRIET treatment groups than in those taking placebo. Dosage reduction or interruption for gastrointestinal events was required in 18.5% of patients in the 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. The incidence of gastrointestinal events was highest early in the course of treatment (with highest incidence occurring during the initial 3 months) and decreased over time. Dosage modifications may be necessary in some cases of gastrointestinal adverse reactions *[see Dosage and Administration section 2.3 in full Prescribing Information]*.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Liver Enzyme Elevations *[see Warnings and Precautions]*
- Photosensitivity Reaction or Rash *[see Warnings and Precautions]*
- Gastrointestinal Disorders *[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 to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of pirfenidone has been evaluated in more than 1400 subjects with over 170 subjects exposed to pirfenidone for more than 5 years in clinical trials.

ESBRIET was studied in 3 randomized, double-blind, placebo-controlled trials (Studies 1, 2, and 3) in which a total of 623 patients received 2403 mg/day of ESBRIET and 624 patients received placebo. Subjects ages ranged from 40 to 80 years (mean age of 67 years). Most patients were male (74%) and Caucasian (95%). The mean duration of exposure to ESBRIET was 62 weeks (range: 2 to 118 weeks) in these 3 trials.

At the recommended dosage of 2403 mg/day, 14.6% of patients on ESBRIET compared to 9.6% on placebo permanently discontinued treatment because of an adverse event. The most common (>1%) adverse reactions leading to discontinuation were rash and nausea. The most common (>3%) adverse reactions leading to dosage reduction or interruption were rash, nausea, diarrhea, and photosensitivity reaction.

The most common adverse reactions with an incidence of ≥10% and more frequent in the ESBRIET than placebo treatment group are listed in Table 1.

Table 1. Adverse Reactions Occurring in ≥10% of ESBRIET-Treated Patients and More Commonly Than Placebo in Studies 1, 2, and 3

Adverse Reaction	% of Patients (0 to 118 Weeks)	
	ESBRIET 2403 mg/day (N = 623)	Placebo (N = 624)
Nausea	36%	16%
Rash	30%	10%
Abdominal Pain[1]	24%	15%
Upper Respiratory Tract Infection	27%	25%
Diarrhea	26%	20%
Fatigue	26%	19%
Headache	22%	19%
Dyspepsia	19%	7%
Dizziness	18%	11%
Vomiting	13%	6%
Anorexia	13%	5%
Gastro-esophageal Reflux Disease	11%	7%
Sinusitis	11%	10%
Insomnia	10%	7%
Weight Decreased	10%	5%
Arthralgia	10%	7%

[1] Includes abdominal pain, upper abdominal pain, abdominal distension, and stomach discomfort.

Adverse reactions occurring in ≥5 to <10% of ESBRIET-treated patients and more commonly than placebo are photosensitivity reaction (9% vs. 1%), decreased appetite (8% vs. 3%), pruritus (8% vs. 5%), asthenia (6% vs. 4%), dysgeusia (6% vs. 2%), and non-cardiac chest pain (5% vs. 4%).

Postmarketing Experience

In addition to adverse reactions identified from clinical trials the following adverse reactions have been identified during postapproval use of pirfenidone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Blood and Lymphatic System Disorders
Agranulocytosis

Immune System Disorders
Angioedema

Hepatobiliary Disorders
Bilirubin increased in combination with increases of ALT and AST

DRUG INTERACTIONS

CYP1A2 Inhibitors

Pirfenidone is metabolized primarily (70 to 80%) via CYP1A2 with minor contributions from other CYP isoenzymes including CYP2C9, 2C19, 2D6 and 2E1.

Strong CYP1A Inhibitors

The concomitant administration of ESBRIET and fluvoxamine or other strong CYP1A2 inhibitors (e.g., enoxacin) is not recommended because it significantly increases exposure to ESBRIET *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*. Use of fluvoxamine or other strong CYP1A2 inhibitors should be discontinued prior to administration of ESBRIET and avoided during ESBRIET treatment. In the event that fluvoxamine or other strong CYP1A2 inhibitors are the only drug of choice, dosage reductions are recommended. Monitor for adverse reactions and consider discontinuation of ESBRIET as needed *[see Dosage and Administration section 2.4 in full Prescribing Information]*.

Moderate CYP1A Inhibitors

Concomitant administration of ESBRIET and ciprofloxacin (a moderate inhibitor of CYP1A2) moderately increases exposure to ESBRIET *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*. If ciprofloxacin at the dosage of 750 mg twice daily cannot be avoided, dosage reductions are recommended *[see Dosage and Administration section 2.4 in full Prescribing Information]*. Monitor patients closely when ciprofloxacin is used at a dosage of 250 mg or 500 mg once daily.

Concomitant CYP1A2 and other CYP Inhibitors

Agents or combinations of agents that are moderate or strong inhibitors of both CYP1A2 and one or more other CYP isoenzymes involved in the metabolism of ESBRIET (i.e., CYP2C9, 2C19, 2D6, and 2E1) should be discontinued prior to and avoided during ESBRIET treatment.

CYP1A2 Inducers

The concomitant use of ESBRIET and a CYP1A2 inducer may decrease the exposure of ESBRIET and this may lead to loss of efficacy. Therefore, discontinue use of strong CYP1A2 inducers prior to ESBRIET treatment and avoid the concomitant use of ESBRIET and a strong CYP1A2 inducer *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: **Pregnancy Category C.**

There are no adequate and well-controlled studies of ESBRIET in pregnant women. Pirfenidone was not teratogenic in rats and rabbits. Because animal reproduction studies are not always predictive of human response, ESBRIET should be used during pregnancy only if the benefit outweighs the risk to the patient.

A fertility and embryo-fetal development study with rats and an embryo-fetal development study with rabbits that received oral doses up to 3 and 2 times, respectively, the maximum recommended daily dose (MRDD) in adults (on mg/m^2 basis at maternal doses up to 1000 and 300 mg/kg/day, respectively) revealed no evidence of impaired fertility or harm to the fetus due to pirfenidone. In the presence of maternal toxicity, acyclic/irregular cycles (e.g., prolonged estrous cycle) were seen in rats at doses approximately equal to and higher than the MRDD in adults (on a mg/m^2 basis at maternal doses of 450 mg/kg/day and higher). In a pre- and post-natal development study, prolongation of the gestation period, decreased numbers of live newborn, and reduced pup viability and body weights were seen in rats at an oral dosage approximately 3 times the MRDD in adults (on a mg/m^2 basis at a maternal dose of 1000 mg/kg/day).

Nursing Mothers

A study with radio-labeled pirfenidone in rats has shown that pirfenidone or its metabolites are excreted in milk. It is not known whether ESBRIET is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue ESBRIET, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness of ESBRIET in pediatric patients have not been established.

Geriatric Use

Of the total number of subjects in the clinical studies receiving ESBRIET, 714 (67%) were 65 years old and over, while 231 (22%) were 75 years old and over. No overall differences in safety or effectiveness were observed between older and younger patients. No dosage adjustment is required based upon age.

ESBRIET® (pirfenidone)

Hepatic Impairment

ESBRIET should be used with caution in patients with mild (Child Pugh Class A) to moderate (Child Pugh Class B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed *[see Dosage and Administration section 2.2 in full Prescribing Information]*.

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 *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*.

Renal Impairment

ESBRIET should be used with caution in patients with mild (CL_{cr} 50–80 mL/min), moderate (CL_{cr} 30–50 mL/min), or severe (CL_{cr} less than 30 mL/min) renal impairment *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*. Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed *[see Dosage and Administration section 2.3 in full Prescribing Information]*. The safety, efficacy, and pharmacokinetics of ESBRIET have not been studied in patients with end-stage renal disease requiring dialysis. Use of ESBRIET in patients with end-stage renal diseases requiring dialysis is not recommended.

Smokers

Smoking causes decreased exposure to ESBRIET *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*, which may alter the efficacy profile of ESBRIET. Instruct patients to stop smoking prior to treatment with ESBRIET and to avoid smoking when using ESBRIET.

OVERDOSAGE

There is limited clinical experience with overdosage. Multiple dosages of ESBRIET up to a maximum tolerated dose of 4005 mg per day were administered as five 267 mg capsules three times daily to healthy adult volunteers over a 12-day dose escalation.

In the event of a suspected overdosage, appropriate supportive medical care should be provided, including monitoring of vital signs and observation of the clinical status of the patient.

PATIENT COUNSELING INFORMATION

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

Liver Enzyme Elevations

Advise patients that they may be required to undergo liver function testing periodically. Instruct patients to immediately report any symptoms of a liver problem (e.g., skin or the white of eyes turn yellow, urine turns dark or brown [tea colored], pain on the right side of stomach, bleed or bruise more easily than normal, lethargy) *[see Warnings and Precautions]*.

Photosensitivity Reaction or Rash

Advise patients to avoid or minimize exposure to sunlight (including sunlamps) during use of ESBRIET because of concern for photosensitivity reactions or rash. Instruct patients to use a sunblock and to wear clothing that protects against sun exposure. Instruct patients to report symptoms of photosensitivity reaction or rash to their physician. Temporary dosage reductions or discontinuations may be required *[see Warnings and Precautions]*.

Gastrointestinal Events

Instruct patients to report symptoms of persistent gastrointestinal effects including nausea, diarrhea, dyspepsia, vomiting, gastro-esophageal reflux disease, and abdominal pain. Temporary dosage reductions or discontinuations may be required *[see Warnings and Precautions]*.

Smokers

Encourage patients to stop smoking prior to treatment with ESBRIET and to avoid smoking when using ESBRIET *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*.

Take with Food

Instruct patients to take ESBRIET with food to help decrease nausea and dizziness.

Manufactured for:
InterMune, Inc.
Brisbane, CA 94005 USA

INTERMUNE®

S. aureus infections in 1.3% hospitalized for CAP

BY JENNIE SMITH
Frontline Medical News

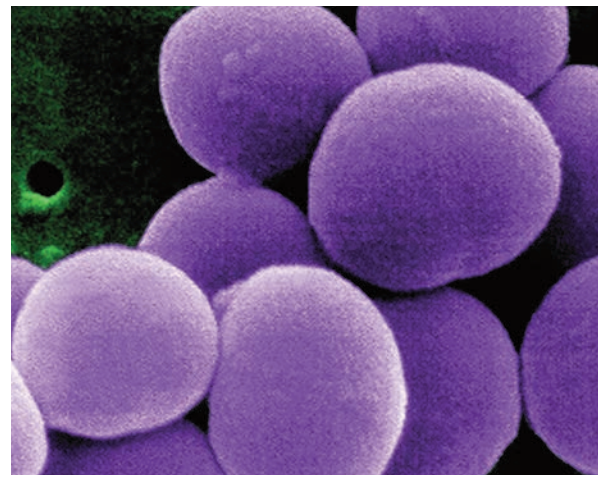
SAN ANTONIO – Slightly more than 1% of children hospitalized with community-acquired pneumonia (CAP) were found to have *Staphylococcus aureus* infections, based on a single-site, retrospective study of 554 children hospitalized with CAP.

The study results, presented at the Pediatric Hospital Medicine 2015 meeting by Dr. Meghan E. Hofto, begin to address concerns about the impact of guidelines that recommend narrow spectrum antibiotics for uncomplicated CAP and reserve third-generation cephalosporins for complicated pneumonias. Those concerns include whether *S. aureus* infections are getting missed and the resulting consequences of the delays in effective treatment for those patients.

The study findings also indicate that certain features at presentation – notably anemia and complications such as pleural effusion, necrosis, and cavitation – might identify a high-risk subgroup.

Seven patients (1.3%) in the study cohort had *S. aureus* infections, and all had been treated in other health care settings prior to admission. Four had been started on amoxicillin, two had received multiple agents, and one had tested positive for influenza virus and was first treated with oseltamavir only, said Dr. Hofto, of Children's of Alabama at the University of Alabama, Birmingham.

Once admitted, however, all patients with *S. aureus* infections were started on vancomycin within 24 hours. The diagnosis was confirmed by pleural fluid culture in five cases, by clinical presentation in one case, and by sputum culture in one case, Dr. Hofto said at the meeting, sponsored by the Society of Hospital Medicine, the American Academy of Pediatrics, the AAP Section on Hospital Medicine, and the Academic Pediatric Association.



©CDC/Janice Haney Carr

If within 48 hours, patients are not responding to first-line treatment, "you should start thinking about other causes," Dr. Hofto said, including *S. aureus,* and starting those patients on alternative antibiotics.

The cohort of 554 patients included 78 with complicated pneumonia, characterized by pleural effusion or cavitation. Six of the seven patients with *S. aureus* infections were recorded as having complicated pneumonia.

Other factors associated with probability of *S. aureus* infection were age (median 18 months vs. 40.5 months for the rest of the cohort) and significantly higher incidence of anemia (*P* less than .01), a finding that Dr. Hofto said was striking.

Within 24 hours of presentation, six out the seven cases with *S. aureus* infections had anemia. Of all 78 patients with complicated disease, 12 had anemia.

Community-acquired *S. aureus* pneumonia has been linked in other studies to severe leukopenia, Dr. Hofto noted (BMC Infect Dis. 2013;13:359) and (Paediatric Respiratory Reviews 2011 Sept;12:182-9).

In an interview, Dr. Hofto said the findings support current guidelines in favor of first-line penicillin, amoxicillin, or ampicillin.

"Part of what we're looking at with guideline adherence is the barriers to treating with empiric narrow spectrum antibiotics – and obviously, one of the things people are concerned about is that we are going to miss something," she said.

"I think we can pretty confidently say that if it's uncomplicated CAP – if there's no pleural effusion, no necrosis, no cavitation – you can treat with narrow spectrum antibiotics, as the likelihood of (*S. aureus* pneumonia) is slim to none."

If within 48 hours, patients are not responding to the first-line treatment, "you should start thinking about other causes," Dr. Hofto said, noting that her review found all *S. aureus* patients were started on effective antibiotics – mostly vancomycin and ceftriaxone – within 24 hours of presentation.

Dr. Hofto noted as a limitation of her study, which used retrospective chart reviews of more than 3,400 children hospitalized for suspected pneumonia over a 3-year period, that additional *S. aureus* cases could have been missed because of a lack of proper coding or microbial confirmation. Another limitation was the single-site design and the small number of *S. aureus* cases.

Dr. Hofto said she is conducting a more in-depth chart review to ensure that no further cases of *S. aureus* CAP were missed in her sample.

The study received no outside funding, and Dr. Hofto disclosed no conflicts of interest.

Mood disorders up complication risk in pneumonia patients

BY JENNIE SMITH
Frontline Medical News

SAN ANTONIO – Pediatric pneumonia patients had a significantly longer length of hospital stay and a higher rate of complications when they also had mood or anxiety disorders, in a study of nearly 35,000 hospitalizations.

Children with chronic complex illnesses have longer hospital stays when they also have mood or anxiety disorders, but less is known about how these disorders affect children hospitalized for more common conditions, Dr. Stephanie Doupnik of Children's Hospital of Philadelphia said at the Pediatric Hospital Medicine 2015 meeting.

She and her colleagues used the 2012 Kids' Inpatient Database to identify 34,795 hospitalizations nationwide for pneumonia among children and adolescents aged 5-20. Of those 13 and older (28% of the cohort), a mood or anxiety diagnosis was recorded at discharge for 9.3%, and in school-age children, for 1.1%. Diagnoses included major depressive disorder, generalized anxiety disorder, and posttraumatic stress disorder.

Pneumonia complications such as respiratory failure, sepsis, and suppuration were seen in 10.7% of the younger children, and 18.7% of those 13 and older.

The odds of experiencing any complication were significantly higher in children with mood and anxiety disorders, regardless of age, the researchers noted. The older children saw an odds ratio of 1.8 (95% confidence interval, 1.3-2.0) and the younger children, 1.6 (95% CI, 13-2.0) (*P* less than .001 for both). Length of stay (LOS) was prolonged among patients with mood and anxiety disorders by 11% in the younger children and by 13% in the adolescents and young adults.

Dr. Doupnik and her colleagues suspected that an increased rate of complications might explain the differences in LOS. In analyzing records for adolescents without complications, they found that LOS was still longer (6.8 vs. 5.4 days) for those with mood disorders. Among adolescents with complications, LOS was still slightly higher in the mood disorder group (4.4 vs. 3.7 days). These differences were statistically significant.

The odds of experiencing any complication were significantly higher in children with mood and anxiety disorders.

DR. DOUPNIK

No statistically significant interaction was seen between complications and a mood or anxiety disorder diagnosis at discharge. "If complications were accounting for that prolonged [LOS], we would have expected differences between those groups," Dr. Doupnik said at the meeting, sponsored by the Society of Hospital Medicine, the American Academy of Pediatrics, the AAP Section on Hospital Medicine, and the Academic Pediatric Association. "Complications do not account for the increase in [LOS] among patients with mood and anxiety disorders," she said.

A lack of granularity in the data "that would allow us to identify other factors that might be contributing to this association," was a study limitation, she said.

Delays in presentation to the hospital could account for the association between mental health disorders and LOS, Dr. Doupnik said in an interview. It is possible "that patients interact differently with staff and providers in the hospital. If they can't cope as well with the things that need to happen during a hospitalization, that could prolong their [LOS] or increase risk of complications."

Dr. Doupnik had no disclosures.

Are you ready?

The power of U — inspired by you.

MAQUET
GETINGE GROUP

It's all about you. Every day your commitment to Respiratory Care excellence shines through in your skill and compassion, making a difference in the lives of your patients and their families.

You are the inspiration for our latest therapeutic innovations. Working closely with Respiratory Care professionals, Maquet develops solutions that speak to your needs for optimal patient care.

We invite you to visit us at AARC Congress 2015, Booth #117 / #906, to experience our latest innovative product offerings and to explore how we can help you advance Respiratory Care — the power of U.

Learn more about AARC Congress 2015
c.aarc.org/education/meetings/congress_15/

At AARC Congress 2015, visit Maquet Booth #117 / #906

www.maquetusa.com

Hypertonic saline might cut bronchiolitis LOS

BY JENNIE SMITH
Frontline Medical News

SAN ANTONIO – Nebulized hypertonic saline has emerged as a promising, low-risk, and low-cost treatment option for bronchiolitis, a disease for which few options exist.

Still, the evidence for hypertonic saline remains inconsistent, with many studies failing to show a clear benefit in clinical scores or length of stay compared with normal saline in children hospitalized for bronchiolitis. Supportive care remains the recommended approach for this patient group.

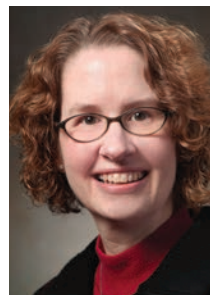
A 2013 Cochrane review of trials comparing normal saline 0.9% with hypertonic saline 3% suggested that hypertonic saline reduced mean hospital length of stay by 1.3 days in children with bronchiolitis as well as improved clinical severity scores. But more recent negative trials have called the Cochrane findings into question.

At the Pediatric Hospital Medicine meeting, Dr. Corinne G. Brooks of the Children's Hospital at Dartmouth-Hitchcock in Lebanon, N.H., presented an updated evaluation of the Cochrane findings as well as several newer studies, which found that study heterogeneity was excessively high, though resolved by accounting for culturally expected length of stay, which varied from 2 to 7 days across studies.

Studies conducted in countries where average length of stay for bronchiolitis in the placebo arm is longer than 3 days reported a greater benefit than did those in countries like the United States,

VIEW ON THE NEWS

Dr. Susan Millard, FCCP comments: This report from the Pediatric Hospital Medicine 2015 Conference analyzes the 2013 Cochrane study. There was also a recent AAP statement regarding the management of bronchiolitis.



The meta-analysis concludes that hypertonic saline nebs may be considered for patients expected to stay longer than 3 days in the hospital. Interestingly, this is probably when a pediatric pulmonary consult would be obtained at many Children's Hospitals!

Because hospital length of stay should be correlated with severity of illness, Dr. Brooks also evaluated respiratory scores available in each study and found that higher scores also correlated with the utility of hypertonic saline.

The two Chinese studies included in the review had particularly long lengths of stay and were conducted in a city with poor air quality, and in which about 70% of patients were on systemic corticosteroids at baseline. "So there's some question as to whether they were even measuring the same disease process," Dr. Brooks told the conference.

She and her colleagues reevaluated the Cochrane data both with and without the two outlying studies from China, and incorporated results from three additional studies not included in the Cochrane review.

Modeling cumulative results using a length of stay typical in the United States, the benefit from hypertonic saline was a reduction of 0.31 days, or 31 days/100 patients.

Dr. Brooks noted that the current data are consistent with two possibilities, that the longer a patient is treated with hypertonic saline, the better it works or that "perhaps hypertonic saline works better for sicker patients – we don't know yet." She acknowledged several limitations of the meta-analysis, including that patient age, additional medications, day of illness at admission, and frequency of treatment could not be correlated.

The existing data "do not support rejecting hypertonic saline for all patients or giving it to all populations," Dr. Brooks told the conference, noting that "there are good physiologic reasons to believe hypertonic saline might have an impact based on its benefits to other respiratory populations such as cystic fibrosis – and it's particularly appealing because of its low risk and low cost."

However, she said, "if we're going to use this intervention intelligently, we need to find where there is and where there isn't a benefit."

Dr. Brooks concluded that hypertonic saline might be worth considering for patients with an expected stay of longer than 3 days or for those with baseline clinical scores higher than average.

Her study received no outside funding.

Routine tests for occult cancer suffice for VTE patients

BY DOUG BRUNK
Frontline Medical News

TORONTO – The prevalence of occult cancer is low in patients with a first unprovoked venous thromboembolism, according to results from a multicenter, randomized study presented at the International Society on Thrombosis and Haemostasis congress.

In addition, routine screening with the addition of a comprehensive CT scan of the abdomen and pelvis was no better than routine screening alone in detecting occult cancer in this population.

Those are key findings that Dr. Marc Carrier of the University of Ottawa presented from the Screening for Occult Malignancy in Patients With Idiopathic Venous Thromboembolism (SOME) trial, a multicenter, open-label, randomized controlled trial that compared the efficacy of conventional screening with or without comprehensive CT of the abdomen/pelvis for detecting occult cancers in patients with unprovoked venous thromboembolism (VTE). The results of this study were published the same day as his presentation in the New England Journal of Medicine.

"It has been described that up to 10% of patients with unprovoked VTE are diagnosed with cancer in the year following their VTE diagnosis," Dr. Carrier said. "Therefore, it's appealing for clinicians to screen these patients for occult cancer but it has led to a lot of great diversity in practices. Some clinicians prefer to use a limited screening strategy that would include a history, physical examination, routine blood tests, and a chest x-ray. Other clinicians prefer to use the limited screening strategy in combination with additional tests. That could be CT of the abdomen and pelvis, ultrasound, or tumor marker, or [computed axial tomography] scan. It's hard for a physician to know what to use."

For the SOME trial, a total of 854 patients with unprovoked VTE were randomized to two groups: 431 to limited occult cancer screening (basic blood work, chest x-ray, and breast/cervical/prostate cancer screening) and 423 to limited screening in combination with a comprehensive CT of the abdomen/pelvis. The comprehensive CT included a virtual colonoscopy and gastroscopy, a biphasic enhanced CT, a parenchymal pancreatogram, and a uniphasic enhanced CT of distended bladder. The primary outcome was confirmed cancer that was missed by the screening strategy and detected by the end of the 1-year follow-up period.

Dr. Carrier reported that 33 patients (3.9%) had a new diagnosis of cancer in the interval between randomization and 1-year follow-up: 14 in the limited-screening group and 19 in the limited-screening-plus-CT group, a difference that was not statistically significant ($P = .28$). In addition, the number of occult cancers missed by the end of the 1-year follow-up period was similar between the two groups: four in the limited-screening group and five in the limited-screening-plus-CT group.

He and his associates also found no significant differences between the limited-screening group and the limited-screening-plus-CT group in the rate of detection of early cancers (0.23% vs. 0.71%, respectively; $P = .37$), in overall mortality (1.4% vs. 1.2%; $P > 0.99$), or in cancer-related mortality (1.4% vs. 0.95%; $P = .75$).

"Occult cancers are not nearly as common as we thought they were, which is reassuring for clinicians and patients because then we don't have to do a lot of investigations to try and find them, and often scare patients and expose them to radiation and additional procedures," Dr. Carrier said in an interview. "Limited screening alone, which is what is recommended in Canada and in the United States for age- and gender-specific screening, is more than reasonable for these patients."

Therese Borden contributed to this article.

dbrunk@frontlinemedcom.com

VITALS

Key clinical point: Occult cancers in patients with a first unprovoked VTE are not nearly as common as previously thought, and limited screening for such cancers is appropriate.

Major finding: There were no significant differences between the limited-screening group and the limited-screening-plus-CT group in the rate of detection of early cancers (0.23% vs. 0.71%); in overall mortality (1.4% vs. 1.2%), or in cancer-related mortality (1.4% vs. 0.95%).

Data source: A multicenter, open-label, randomized controlled trial of 854 patients with unprovoked VTE.

Disclosures: The trial was funded by the Heart and Stroke Foundation of Canada. Dr. Carrier reported having no financial disclosures.

VTE recurrence risk persists for at least 3 years

BY SHARON WORCESTER
Frontline Medical News

TORONTO – The risk of recurrence following an initial episode of venous thromboembolism is highest in the first 3 months, but remains high for up to 3 years, according to findings from a population-based study involving 2,989 adults.

Over a mean of 23 months (median, 30 months), there were 329 VTE recurrences in the study subjects. Cumulative incidence rates were 5.1% at 3 months, and 14.5% at 3 years. The corresponding rates were 8.7% and 24.8% among those with active cancer, 5.2% and 13.0% among those with provoked VTE, and 3.8% and 13.1% among those with unprovoked VTE, Dr. Wei Huang reported at the International Society on Thrombosis and Haemostasis congress.

Cumulative incidence rates were 8.7% at 3 months and 24.8% at 3 years among those with active cancer.

DR. HUANG

Independent predictors of recurrence within 3 years after the index event were active cancer with chemotherapy (hazard ratio, 2.59), active cancer without chemotherapy (HR, 1.59), hypercoagulable state (HR, 2.53), superficial thrombophlebitis (HR, 1.62), varicose vein stripping (HR, 1.75), and inferior vena cava (IVC) filter placement (HR, 2.04), said Dr. Huang of the University of Massachusetts, Worcester.

Individuals included in the study were all residents of the Worcester Metropolitan Statistical Area (WMSA) who had a validated diagnosis of acute first-time deep vein thrombosis and/or pulmonary embolism in a hospital or ambulatory care center that provided short-term care for WMSA residents between 1999 and 2009. Medical records and national and local death registry data were reviewed to examine outcomes up to 3 years after the index event.

Subjects were adults with a mean age of 64 years; 44% were men, and 94% where white. Pulmonary embolism with or without deep vein thrombosis occurred in 42%, and 17% of cases were associated with cancer, 43% involved provoked VTE, and 40% involved unprovoked VTE.

Provoked VTE was defined as VTE occurring within 3 months of a prior surgery, pregnancy, trauma, fracture, or hospitalization in patients without presence of active cancer.

Though limited by the lack of information about variations in physician practices across regions, and by the high proportion of white resident in the WMSA, which both raise questions about whether the findings are generalizable to the U.S. population, the identification of these predictors could allow for improved estimation of risk for individual patients, and may aid in the design of new interventional studies, Dr. Huang concluded.

sworcester@frontlinemedcom.com

VITALS

Key clinical point: The risk of recurrence following an initial episode of venous thromboembolism is highest in the first 3 months, but remains high for up to 3 years, according to findings from a population-based study involving 2,989 adults.

Major finding: Active cancer with chemotherapy was the strongest predictor of VTE recurrence (hazard ratio, 2.59).

Data source: Population-based surveillance of 2,989 adults patients.

Disclosures: The National Institutes of Health supported the study.

For the long-term, once-daily, maintenance bronchodilator treatment in patients with chronic obstructive pulmonary disease (COPD)

Prescribe INCRUSE ELLIPTA one inhalation, once daily

& help patients add more breath to their day

Indication

- INCRUSE ELLIPTA is an anticholinergic indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Important Safety Information for INCRUSE ELLIPTA

CONTRAINDICATIONS

- The use of INCRUSE ELLIPTA is contraindicated in patients with severe hypersensitivity to milk proteins or who have hypersensitivity to umeclidinium or any of the excipients.

WARNINGS AND PRECAUTIONS

- INCRUSE ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.
- INCRUSE ELLIPTA 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.
- If paradoxical bronchospasm occurs, discontinue INCRUSE ELLIPTA and institute alternative therapy.
- Use with caution in patients with narrow-angle glaucoma. Instruct patients to contact a physician immediately if signs or symptoms of acute narrow-angle glaucoma develop.
- Use with caution in patients with urinary retention, especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to contact a physician immediately if signs or symptoms of urinary retention develop.

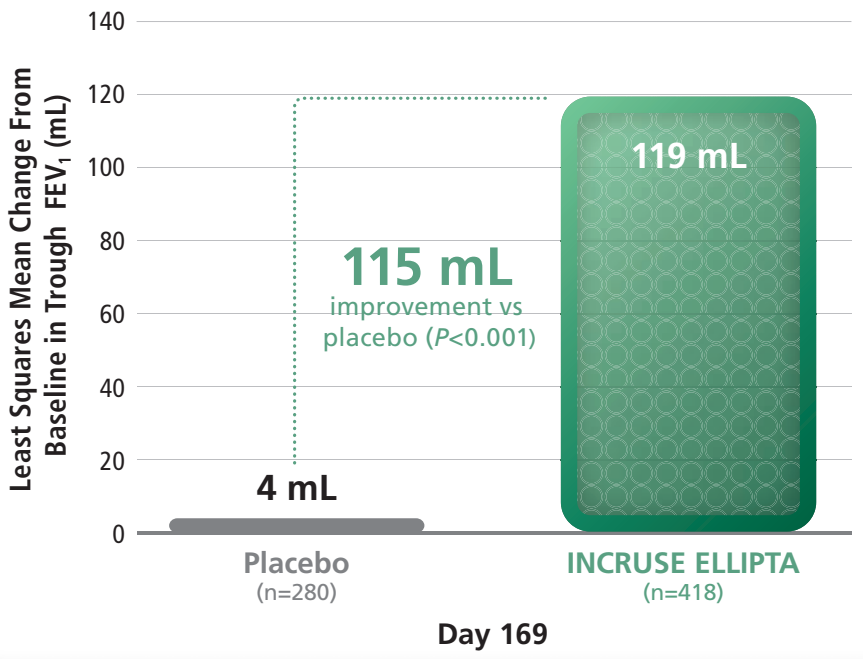
ADVERSE REACTIONS

- The most common adverse reactions (≥1% and more common than placebo) reported in one 12-week and one 24-week clinical trial with INCRUSE ELLIPTA (and placebo) were: nasopharyngitis, 8% (7%); upper respiratory tract infection, 5% (4%); pharyngitis, 1% (<1%); viral upper respiratory tract infection, 1% (<1%); cough, 3% (2%); arthralgia, 2% (1%); myalgia, 1% (<1%); upper abdominal pain, 1% (<1%); toothache, 1% (<1%); contusion, 1% (<1%); tachycardia, 1% (<1%). Other adverse reactions with INCRUSE ELLIPTA observed with an incidence <1% but more common than placebo included atrial fibrillation.

Once-daily INCRUSE ELLIPTA

Helps Improve Breathing in Patients With COPD

Primary Endpoint: Trough (Predose) FEV_1 at Day 169[1,2]



- Results from a 6-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group study that compared the efficacy and safety of INCRUSE ELLIPTA and placebo, each administered once daily by the ELLIPTA Inhaler. The primary endpoint was defined as the mean of the FEV_1 values obtained 23 and 24 hours after dosing on Day 168[1]

Provided improvement in health-related quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ)

- In the same 6-month study, INCRUSE ELLIPTA demonstrated an improvement in health-related quality of life, as measured by a decrease in mean SGRQ total score of 4.69 units, compared with placebo at Day 168
- The proportion of patients with a clinically meaningful decrease (defined as a decrease of at least 4 units from baseline) at Week 24 was greater for INCRUSE ELLIPTA (42%; 172/410) compared with placebo (31%; 86/274)
- These endpoints were not adjusted for multiple comparisons
- The SGRQ is a respiratory disease-specific, patient-reported instrument that measures symptoms, activities, and impact on daily life[3]

Important Safety Information for INCRUSE ELLIPTA (cont'd)

ADVERSE REACTIONS (cont'd)

- In addition to the two placebo-controlled clinical trials with INCRUSE ELLIPTA, a 12-month trial evaluated the safety of umeclidinium 125 mcg in subjects with COPD. Adverse reactions (incidence ≥1% and exceeded that in placebo) in subjects receiving umeclidinium 125 mcg were: nasopharyngitis, upper respiratory tract infection, urinary tract infection, pharyngitis, pneumonia, lower respiratory tract infection, rhinitis, supraventricular tachycardia, supraventricular extrasystoles, sinus tachycardia, idioventricular rhythm, headache, dizziness, sinus headache, cough, back pain, arthralgia, pain in extremity, neck pain, myalgia, nausea, dyspepsia, diarrhea, rash, depression, and vertigo.

DRUG INTERACTIONS

- Avoid coadministration of INCRUSE ELLIPTA with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects.

References: 1. Donohue JF, Maleki-Yazdi MR, Kilbride S, et al. Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD. *Respir Med.* 2013;107(10):1538-1546. **2.** Data on file, GSK. **3.** Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. *Respir Med.* 1991;85 (suppl B):25-31.

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

www.GSKSource.com

INCRUSE® ELLIPTA®
(umeclidinium 62.5 mcg inhalation powder)

BRIEF SUMMARY

INCRUSE® ELLIPTA®
(umeclidinium inhalation powder)
FOR ORAL INHALATION USE
The following is a brief summary only; see full prescribing information for complete product information.

1 INDICATIONS AND USAGE
INCRUSE ELLIPTA is an anticholinergic indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

4 CONTRAINDICATIONS
The use of INCRUSE ELLIPTA is contraindicated in the following conditions: severe hypersensitivity to milk proteins or hypersensitivity to umeclidinium or any of the excipients *[see Warnings and Precautions (5.3), Description (11) of full prescribing information]*.

5 WARNINGS AND PRECAUTIONS

5.1 Deterioration of Disease and Acute Episodes
INCRUSE ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD. INCRUSE ELLIPTA has not been studied in subjects with acutely deteriorating COPD. The initiation of INCRUSE ELLIPTA in this setting is not appropriate.
INCRUSE ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. INCRUSE ELLIPTA 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.
COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If INCRUSE ELLIPTA no longer controls symptoms of bronchoconstriction; the patient's inhaled, short-acting $beta_2$-agonist becomes less effective; or the patient needs more short-acting $beta_2$-agonist than usual, these may be markers of deterioration of disease. In this setting a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of INCRUSE ELLIPTA beyond the recommended dose is not appropriate in this situation.

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

5.3 Hypersensitivity Reactions
Hypersensitivity reactions may occur after administration of INCRUSE ELLIPTA. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder products containing lactose; therefore, patients with severe milk protein allergy should not use INCRUSE ELLIPTA *[see Contraindications (4)]*.

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

5.5 Worsening of Urinary Retention
INCRUSE ELLIPTA should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately if any of these signs or symptoms develops.

6 ADVERSE REACTIONS
The following adverse reactions are described in greater detail in other sections:
- Paradoxical bronchospasm *[see Warnings and Precautions (5.2)]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.4)]*
- Worsening of urinary retention *[see Warnings and Precautions (5.5)]*

6.1 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 1,663 subjects with COPD across 8 clinical trials (mean age: 62.7 years; 89% white; 65% male across all treatments, including placebo) received at least 1 inhalation dose of umeclidinium at doses of 62.5 or 125 mcg. In the 4 randomized, double-blind, placebo- or active-controlled, efficacy clinical trials, 1,185 subjects received umeclidinium for up to 24 weeks, of which 487 subjects received the recommended dose of umeclidinium 62.5 mcg. In a 12-month, randomized, double-blind, placebo-controlled, long-term safety trial, 227 subjects received umeclidinium 125 mcg for up to 52 weeks *[see Clinical Studies (14) of full prescribing information]*.
The incidence of adverse reactions associated with INCRUSE ELLIPTA in Table 1 is based upon 2 placebo-controlled efficacy trials: one 12-week trial and one 24-week trial.

Table 1. Adverse Reactions With INCRUSE ELLIPTA With ≥1% Incidence and More Common Than With Placebo in Subjects With Chronic Obstructive Pulmonary Disease

Adverse Reaction	INCRUSE ELLIPTA (n = 487) %	Placebo (n = 348) %
Infections and infestations		
Nasopharyngitis	8%	7%
Upper respiratory tract infection	5%	4%
Pharyngitis	1%	<1%
Viral upper respiratory tract infection	1%	<1%
Respiratory, thoracic, and mediastinal disorders		
Cough	3%	2%
Musculoskeletal and connective tissue disorders		
Arthralgia	2%	1%
Myalgia	1%	<1%
Gastrointestinal disorders		
Abdominal pain upper	1%	<1%
Toothache	1%	<1%
Injury, poisoning, and procedural complications		
Contusion	1%	<1%
Cardiac disorders		
Tachycardia	1%	<1%

Other adverse reactions with INCRUSE ELLIPTA observed with an incidence less than 1% but more common than placebo included atrial fibrillation.
In a long-term safety trial, 336 subjects (n = 227 umeclidinium 125 mcg, n = 109 placebo) were treated for up to 52 weeks with umeclidinium 125 mcg or placebo. The demographic and baseline characteristics of the long-term safety trial were similar to those of the efficacy trials described above. Adverse reactions that occurred with a frequency greater than or equal to 1% in subjects

receiving umeclidinium 125 mcg that exceeded that in placebo in this trial were: nasopharyngitis, upper respiratory tract infection, urinary tract infection, pharyngitis, pneumonia, lower respiratory tract infection, rhinitis, supraventricular tachycardia, supraventricular extrasystoles, sinus tachycardia, idioventricular rhythm, headache, dizziness, sinus headache, cough, back pain, arthralgia, pain in extremity, neck pain, myalgia, nausea, dyspepsia, diarrhea, rash, depression, and vertigo.

7 DRUG INTERACTIONS

7.1 Anticholinergics

There is potential for an additive interaction with concomitantly used anticholinergic medicines. Therefore, avoid coadministration of INCRUSE ELLIPTA with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects *[see Warnings and Precautions (5.4, 5.5), Adverse Reactions (6)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled trials with INCRUSE ELLIPTA in pregnant women. Because animal reproduction studies are not always predictive of human response, INCRUSE ELLIPTA 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 INCRUSE ELLIPTA.

8.2 Labor and Delivery

There are no adequate and well-controlled human trials that have investigated the effects of INCRUSE ELLIPTA during labor and delivery. INCRUSE ELLIPTA should be used during labor only if the potential benefit justifies the potential risk.

8.3 Nursing Mothers

It is not known whether INCRUSE ELLIPTA is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when INCRUSE ELLIPTA is administered to a nursing woman. Since there are no data from well-controlled human studies on the use of INCRUSE ELLIPTA by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue INCRUSE ELLIPTA, taking into account the importance of INCRUSE ELLIPTA to the mother.
Subcutaneous administration of umeclidinium to lactating rats at approximately 25 times the MRHDID in adults resulted in a quantifiable level of umeclidinium in 2 pups, which may indicate transfer of umeclidinium in milk.

8.4 Pediatric Use

INCRUSE ELLIPTA is not indicated for use in children. The safety and efficacy in pediatric patients have not been established.

8.5 Geriatric Use

Based on available data, no adjustment of the dosage of INCRUSE ELLIPTA in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.
Clinical trials of INCRUSE ELLIPTA included 810 subjects aged 65 years and older, and, of those, 183 subjects were aged 75 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

Patients with moderate hepatic impairment (Child-Pugh score of 7-9) showed no relevant increases in C_{max} or AUC, nor did protein binding differ between subjects with moderate hepatic impairment and their healthy controls. Studies in subjects with severe hepatic impairment have not been performed *[see Clinical Pharmacology (12.3) of full prescribing information]*.

8.7 Renal Impairment

Patients with severe renal impairment (creatinine clearance less than 30 mL/min) showed no relevant increases in C_{max} or AUC, nor did protein binding differ between subjects with severe renal impairment and their healthy controls. No dosage adjustment is required in patients with renal impairment *[see Clinical Pharmacology (12.3) of full prescribing information]*.

10 OVERDOSAGE

No case of overdose has been reported with INCRUSE ELLIPTA.
High doses of umeclidinium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a once-daily inhaled dose of up to 1,000 mcg umeclidinium (16 times the maximum recommended daily dose) for 14 days in subjects with COPD.
Treatment of overdosage consists of discontinuation of INCRUSE ELLIPTA together with institution of appropriate symptomatic and/or supportive therapy.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Umeclidinium produced no treatment-related increases in the incidence of tumors in 2-year inhalation studies in rats and mice at inhaled doses up to 137 and 295/200 mcg/kg/day (male/female), respectively (approximately 20 and 25/20 times the MRHDID in adults on an AUC basis, respectively).
Umeclidinium tested negative in the following genotoxicity assays: the *in vitro* Ames assay, *in vitro* mouse lymphoma assay, and *in vivo* rat bone marrow micronucleus assay.
No evidence of impairment of fertility was observed in male and female rats at subcutaneous doses up to 180 mcg/kg/day and inhaled doses up to 294 mcg/kg/day, respectively (approximately 100 and 50 times, respectively, the MRHDID in adults on an AUC basis).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
Not for Acute Symptoms: Inform patients that INCRUSE ELLIPTA is not meant to relieve acute symptoms of COPD and extra doses should not be used for that purpose. Advise them to treat acute symptoms with a rescue inhaler such as albuterol. Provide patients with such medicine and instruct them in how it should be used.
Instruct patients to seek medical attention immediately if they experience any of the following:
- Symptoms get worse
- Need for more inhalations than usual of their rescue inhaler

Patients should not stop therapy with INCRUSE ELLIPTA without physician/provider guidance since symptoms may recur after discontinuation.
Paradoxical Bronchospasm: As with other inhaled medicines, INCRUSE ELLIPTA can cause paradoxical bronchospasm. If paradoxical bronchospasm occurs, instruct patients to discontinue INCRUSE ELLIPTA.
Worsening of Narrow-Angle Glaucoma: Instruct patients to be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately if any of these signs or symptoms develops.
Worsening of Urinary Retention: Instruct patients to be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination). Instruct patients to consult a physician immediately if any of these signs or symptoms develops.

GSK
Research Triangle Park, NC 27709

Revised: 6/2014 INC:3BRS

Hospital clinicians commonly work while sick

BY TARA HAELLE
Frontline Medical News

The vast majority of doctors and other trained medical professionals at a hospital went to work while sick within the past year, even though they realized the risk that decision places on patients, according to a recent study.

In fact, almost 1 in 10 hospital clinicians worked while sick at least five times in the past year, primarily because of staffing concerns or not wanting to let colleagues down, reported Julia Szymczak, Ph.D., of Children's Hospital of Philadelphia (JAMA Pediatr. 2015 Jul 6. doi: 10.1001/jamapediatrics.2015.0684).

"A combination of closed- and open-ended questions illustrated that the decision to work while sick was shaped by systems-level and sociocultural factors that interacted to cause our respondents to work while symptomatic, despite recognizing that this choice may put patients and colleagues at risk," wrote Dr. Szymczak and colleagues.

©NANDYPHOTOS/THINKSTOCK.COM

They sent out 929 surveys; 538 clinicians responded, including 280 of 459 physicians (61%) and 256 of 470 advanced-practice clinicians (54.5%). The advanced-practice clinicians included registered nurses, physician assistants, clinical nurse specialists, registered nurse anesthetists, and certified nurse midwives. Of those who responded, 15.7% worked in intensive care, 13.1% in surgery, 12.5% in general pediatrics, and 44.8% in another pediatric subspecialty.

Although 95.3% of respondents believed working while sick put patients at risk, 83.1% reported having done so at least once in the past year. Further, that proportion included 52% of all respondents who reported coming to work sick twice in the past year and 9.3% who worked while ill at least five times in the past year.

Nearly a third of respondents said they would work even if they had diarrhea (30%), while 16% said they would work with a fever, and 55.6% would work with acute respiratory symptoms, including cough, congestion, rhinorrhea, and sore throat.

But doctors were more likely than were other professionals to say they would go to work with these symptoms: 38.9% of doctors would work despite diarrhea, compared with 19.9% of advanced-practice clinicians. Doctors and advanced-practice clinicians would work with acute respiratory symptoms (60% vs. 50.8%, respectively), a fever only (21.8% vs. 9.8%), and fever and chills with body aches (18.6% vs. 10.9%, all $P < .03$).

Nearly all respondents (98.7%) said they worked while sick because they did not want to let their colleagues down, and almost all of them worried the hospital would not have enough staff (94.9%) or that they would let their patients down (92.5%).

Smaller majorities of respondents also worked because others also work while sick (65%), worried their colleagues would ostracize them (64%) if they didn't work, were concerned about continuity of care (63.8%), had unsupportive leadership (56.2%), or believed they could not be easily replaced (52.6%).

Among the 316 respondents who filled in additional reasons, 64.9% said they had a very hard time finding someone to cover their shift, 61.1% described a strong cultural norm to work unless extremely sick, and 57% expressed uncertainty about what is considered "too sick to work."

The Centers for Disease Control and Prevention funded the research. The authors reported no disclosures.

VIEW ON THE NEWS

When health care workers are sick, first do no harm

For centuries, a guiding principle for health care workers has been *primum non nocere*, or first do no harm. However, health care workers do exactly that when they work with patients while ill themselves with contagious infections. Even common but untreatable infectious like enterovirus and respiratory syncytial virus can prove deadly to immunocompromised patients.

The propensity to work while ill is influenced by cultural trends. In past years, many ill physicians worked even to the point of receiving intravenous fluids while on the job; working while sick was regarded as a badge of courage. Dr. Szymczak and colleagues identified as an issue the absence of an effective sick relief system that has sufficient flexibility to "staff up" during high rates of health care worker illness. Sick relief systems and policies need to be clear regarding when health care workers should stay away from work, how patient coverage will be ensured, and the availability of and access to paid sick leave.

Determining what constitutes being too sick to work is complicated and lacks a sufficient evidence base. Using a system that bases work restrictions on the presence of key symptoms may add clarity and enable health care workers to recognize when they need to stay home.

Creating a safer and more equitable system of sick leave for health care workers requires a culture change in many institutions to decrease the stigma – internal and external – associated with health care worker illness. Identifying solutions to prioritize patient safety must factor in workforce demands and variability in patient census and emphasize flexibility. Strong administrative and physician leadership and creativity are essential to support appropriate sick leave and ensure adequate staffing. Hospital leadership must ensure that the culture supports a paid sick leave policy that is adequate and nonpunitive.

These comments are selected from an accompanying editorial (JAMA Pediatr. 2015 July 6 [doi:10.1001/jamapediatrics.2015.0994]), written by Dr. Jeffrey R. Starke of the department of pediatrics at Baylor College of Medicine in Houston, and Dr. Mary Anne Jackson of the division of infectious diseases at Children's Mercy Hospital, University of Missouri–Kansas City. Dr. Starke and Dr. Jackson reported no disclosures.

Be aware of 'gotcha' clauses in managed care contracts

BY ALICIA GALLEGOS
Frontline Medical News

CHICAGO – Too often, physicians sign managed care contracts without negotiating or truly understanding all the terms. The complex clauses – or lack thereof – can come back to bite doctors in the form of delayed payments, sudden policy changes, and termination woes, health law attorney Mark S. Kopson warned at a conference held by the American Bar Association.

To avoid these unwelcome surprises, prepare for contract discussions well before the conversation starts, Mr. Kopson advised.

"Don't go into any negotiation unless you know two things. The first is what your starting position will be and, equally if not more important, is what is your ultimate line in the sand?" said Mr. Kopson, who practices in Bloomfield Hills, Mich. "If you go in there not knowing those answers, you're liable to give away the store or not get what you really need."

One major "gotcha" is an insurer that does not reveal upfront that it is not the actual payer, Mr. Kopson said. Some national companies that enter into contracts with doctors are basically network aggregators that negotiate price discounts but then sell the network to the health insurance marketplace, he explained. Physicians later realize their contract states that the company is not responsible for paying claims and that the doctor does not have a contract directly with the payer.

"This is a really big issue that I've been seeing more and more frequently," Mr. Kopson said at the meeting. "If you don't have a direct contract with the payer, you have the possibility of not being able to force payment obligations against the responsible party."

Specify in your contract that the plan must require the payer to pay, he said. That way, if a payer fails to pay, the plan has breached its contract obligation.

Contract terms that involve medical necessity also can lead to frustration

Continued on following page

Continued from previous page

if not properly negotiated. In some cases, the fine print states that medical necessity will be determined by the plan's medical director or otherwise will be ultimately decided by the payer. Instead, include language specifying that a treating physician's professional opinion will be entitled to great deference if medical necessity comes into question, Mr. Kopson said.

The process surrounding clean claims is often overlooked by physicians during contract negotiations, he added. The "gotcha" occurs when a plan retains full control over how contested claims are handled.

"If you don't adequately address this in the contract, you wind up with the payer taking multiple bites of the apple," Mr. Kopson said.

Make sure to clarify parameters

ALICIA GALLEGOS/FRONTLINE MEDICAL NEWS

Know your starting point and your "line in the sand" in negotiations, and have an exit strategy, said Mark S. Kopson.

for how long insurers have to request additional information about a claim and whether they must pay a portion of the claim that is being contested, he advised. Include a firm time line of when payers must complete their review and address payment after the requested information is provided.

Another critical issue: changes to the contract. In some cases, doctors enter into a contract with a plan and then the plan decides some details aren't working out and makes changes. The physician later learns that the contract language allowed the plan to make unilateral changes. In other instances, a plan institutes new products and doctors learn that they had only a certain timeframe to opt out.

To avoid these situations, specify during contract negotiations that policies in conflict with the contract are prohibited, that contract changes can be made only bilaterally, and that unless you directly opt-in to new products, you will not participate.

Mr. Kopson encouraged physicians to have a solid exit strategy in their contracts and to ensure terms regarding contract termination are clearly understood. Clearly defined criteria around "cause" for termination are imperative, he said. In addition, if a plan alleges a termination breach, require it to send a written notice to a specific person/title and ensure that the notice also is provided to counsel.

The bottom line: To avoid trouble later, strongly negotiate at the start of a managed care contract, Mr. Kopson said.

"If you don't ask, if you don't negotiate it in there, you're not going to have that weapon," he said.

agallegos@frontlinemedcom.com
On Twitter @legal_med

Pending court cases can affect laws, billing rules

BY ALICIA GALLEGOS
Frontline Medical News

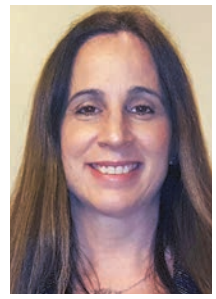
Three cases winding their way through the courts could reshape the Stark Law, the Anti-kickback Statute, and the 60-day federal overpayment rule, and may affect billing practices, practices arrangements, and federal reporting obligations, according to legal experts.

Council for Urological Interests v. Sylvia Burwell et al.

Summary: The case centers on whether the federal Stark Law can prevent physicians from referring patients to hospitals to which the physicians lease equipment. In 2008, the U.S. Department of Health & Human Services prohibited physicians who lease medical equipment to hospitals from referring their Medicare patients to these hospitals for outpatient care involving that

equipment. The regulation prohibits physicians from charging hospitals for the leased equipment on a "per-click," basis. In 2009, the nonprofit Council for Urological Interests sued, claiming the text and legislative history of the Stark Law preclude the HHS from enforcing the per-click ban. The regulation limits the ability of physicians who own joint ventures to refer their patients to receive services under these arrangements, the plaintiffs said. A district court ruled in favor of the HHS, and the Council appealed. A spokeswoman for the U.S. Department of Justice declined to comment for this story.

Case status: In June 2015, the U.S. Court of Appeals for the District of Columbia Circuit ruled that the HHS must reconsider its per-click referral ban. The court suggested that the agency misconstrued the legislative history of the Stark Law to enact the rule.



The outcome will determine whether physicians can engage in per-click leases under Stark Law.

MS. ADLER

Why doctors should care: The ultimate outcome of the case will determine if physicians can engage in

Continued on following page

Continued from previous page

per-click leases under Stark Law, said Chicago health law attorney Ericka L. Adler.

"When HHS changed the regulations to no longer allow the per-click arrangement where physicians were self-referring, it caused a lot of deals to be undone," Ms. Adler said in an interview. These lease arrangements could "be restructured to look more like normal leases and meet the Stark equipment lease exception, but in some cases it created hardships, such as in rural areas."

Meanwhile, the appeals court ruling means the per-click ban cannot be enforced while the government reconsiders, which is good for physicians, said Washington health lawyer Thomas L. Mills, who represented the Council for Urological Interests.

"CMS' permitting per-click leases to non–physician-owned companies while banning them for physician-owned entities made no sense, particularly when the medical procedure is not susceptible to overuse," he said in an interview.

"The [appeals] decision is a victory for the rule of law. It shows that CMS does not have carte blanche to disadvantage physicians by steering control of the implements of their practices to less important participants in the health care delivery system.

United States v. Continuum Health Partners Inc.

Summary: The federal government contends that three hospitals failed to return overpayments to Medicaid in violation of an Affordable Care Act requirement that they be reported and repaid within 60 days of identification. The government alleges that because of a computer glitch, three hospitals operated by Continuum Health Partners Inc. billed both the government and a managed care organization for the same services. After the New York State Comptroller's Office alerted Continuum to a possible overbilling, Continuum did an internal investigation and allegedly found 900 potentially improper Medicaid claims totaling $1 million, according to court documents. The government claims that Continuum failed to repay the overpayments within 60 days and instead repaid only "small batches" of the affected claims over the next 2 years. Continuum argues that the hospitals did not knowingly conceal the overpayments from the government and that the overbillings had not been officially identified. Continuum argues there is only evidence that administrators discussed potential overpayments. The "mere notice of a potential overpayment does not give rise to an established duty until 60 days after the overpayment is

Continued on following page

Continued from previous page

identified," Continuum said in court documents. Attorneys for the government and for Continuum did not return messages seeking comment.

Case status: The case is before the U.S. District Court for the Southern District of New York.

Why doctors should care: The case will provide significant guidance about the ACA 60-day overpayment rule, said Houston health lawyer Micheal E. Clark, who chairs the America Bar Association Health Law Section. The federal rule is unclear, leading to confusion about reporting obligations, he said.

'The agency hasn't defined 'knowing,' what is reasonable knowledge of a known overpayment.'

MR. CLARK

"The agency hasn't really defined what is 'knowing,' what is reasonable knowledge of a known overpayment," Mr. Clark said in an interview. "[The ruling] will be very informative about what this is actually going to mean."

Ameritox v. Millennium Laboratories

Summary: Ameritox revolves around whether a laboratory's giveaway of urine specimen cups to physicians amounted to an illegal kickback. In 2012, lab testing company Ameritox sued Millennium in a Florida district court, alleging that Millennium harmed its business by giving the urine cups to doctors in violation of the Stark Law. Physicians used the cups – which have chemically activated strips that contain patient information – to monitor patients' use of pain medications. Millennium unlawfully obtained physician referrals through free cup agreements, according to

The case highlights the broad spectrum of 'remuneration,' regarding free items or services to doctors.

MS. DRESEVIC

Ameritox's complaint. A federal jury found Millennium had violated the Stark Law and the Anti-Kickback Statute by providing the free cups in exchange for referrals and Ameritox was awarded $11 million. Attorneys for both parties did not return messages seeking comment.

Case status: Millennium appealed, and the case is before the 11th U.S. Circuit Court of Appeals. The U.S. Justice Department has weighed in on the side of Ameritox, arguing that the cup giveaway violated Stark Law and the Anti-Kickback Statute.

Why doctors should care: This case makes it clear that doctors should never accept free point-of-care testing cups or similar medical equipment from a lab, said health lawyer Adrienne Dresevic of Southfield, Mich. The case highlights the broad spectrum of "remuneration," regarding free items or services to doctors, she noted.

"Physicians need to know how to look beyond what the laboratory representative is presenting to them and make their own determinations, sometimes with the help of health care counsel, regarding the legality of a particular arrangement," she said.

agallegos@frontlinemedcom.com
On Twitter @legal_med

Now there is a screening tool you can count on.

SNS Swiss Narcolepsy Scale

A sensitive and specific screening tool for narcolepsy with cataplexy*

5 Questions ▪ Validated ▪ Easy to interpret

For more information or to order the SNS for your office, visit **SwissNarcolepsyScale.com.**

***Shown to have 96% sensitivity and 98% specificity for narcolepsy with cataplexy.**

1. Sturzenegger C, Bassetti CL. The clinical spectrum of narcolepsy with cataplexy: a reappraisal. *J Sleep Res.* 2004;13(4):395-406.
2. Bassetti CL. Spectrum of narcolepsy. In: Baumann CR, Bassetti CL, Scammell TE, eds. *Narcolepsy: Pathophysiology, Diagnosis, and Treatment.* New York, NY: Springer Science+Business Media; 2011:309-319.

Jazz Pharmaceuticals®

ABIM-ACCME links MOC credits, CME activities

BY ALICIA GALLEGOS
Frontline Medical News

The American Board of Internal Medicine (ABIM) and the Accreditation Council for Continuing Medical Education (ACCME) have announced a partnership that aims to unify continuing education activities with Maintenance of Certification (MOC) requirements and expand doctors' options for MOC credit.

As part of the change, ABIM will no longer require CME providers to submit applications to ABIM for activity approval and peer review. Instead, accredited CME providers can use a shared system to record information about CME and ABIM MOC activities. The network will provide additional choices for internists without adding new ACCME requirements, according to an Aug. 12 ABIM announcement.

The American College of Physicians (ACP) praised the move, saying it will provide internists more choices.

"The American College of Physicians has long advocated for a process that gives MOC credit for activities that physicians are already doing," Dr. Wayne J. Riley, ACP president, said in an interview. "We support an easier process and more options for diplomates to get credit for the Part 2 (Self-Assessment of Knowledge) component of MOC."

While ABIM already offers more than 300 medical knowledge options to physicians engaged in MOC, diplomates wanted a more streamlined process that enabled them to more seamlessly combine their ongoing educational activities with MOC requirements, ABIM President Richard J. Baron said in a statement.

"By collaborating with ACCME, ABIM will open the door to even more options for physicians engaged in MOC and will allow them to get MOC credit for high-quality CME activities they are already doing," Dr. Baron said in the statement.

ABIM noted that accredited CME providers in the ACCME system already use the ACCME Program and Activity Reporting System (PARS) to enter data about CME activities. With the new partnership, CME providers can also use PARS to register activities for ABIM MOC. CME administrators can submit learner data and attest to compliance with ABIM-specific requirements for the Medical Knowledge Assessment Recognition Program. ABIM and ACCME will start beta testing the technology later this month, and the associations expect to open the process for accredited CME providers by the end of 2015.

Additionally, ACCME will maintain on its website a list of activities that meet ABIM requirements and that are registered for MOC credit. Data verifying that doctors have completed CME activities will be communicated to ABIM through PARS.

"This collaboration will generate many more opportunities for accredited CME providers to serve as a strategic resource by delivering relevant, effective, independent, practice-based education that counts for MOC," ACCME President Graham T. McMahon said in the statement. "I look forward to working together with ABIM, our community of accredited CME providers, and our community of diplomates to leverage the power of education to drive quality in our medical profession and improve care for the patients we serve."

'By collaborating with ACCME, ABIM will open the door to even more options for physicians engaged in MOC.'

DR. BARON

The partnership is the latest in an ongoing series of modifications to ABIM's MOC process. Earlier this month, ABIM announced that physicians who do not enroll in its MOC program will no longer automatically lose their board certification status. In July, the board announced that no disciplines within its MOC program will require underlying certification and that all diplomates can choose the certifications they wish to maintain. The policy goes into effect Jan. 1, 2016.

In early June, ABIM rolled out changes to its exam outline and score report. Starting with spring 2015 exams, physicians will receive enhanced score reports with more performance details, according to ABIM. The board also updated its internal medicine MOC blueprint – the exam content outline – to ensure that the exam reflects how internists are practicing today and to provide more detailed explanations of topics that may be included in the exam.

The growing list of changes follows a February announcement by ABIM apologizing to physicians for an MOC program that "clearly got it wrong." ABIM pledged to make the program more consistent with physicians' practice and values. Among the immediate changes are updates to its internal medicine exam; suspension of the practice assessment, patient voice, and patient safety requirements for at least 2 years; and setting MOC enrollment fees at or below 2014 levels through at least 2017.

agallegos@frontlinemedcom.com
On Twitter @legal_med

Feedback drives changes to board certification requirement

BY DR. SERPIL C. ERZURUM, FCCP

FOR THE ABIM PULMONARY DISEASE BOARD

Recently, the American Board of Internal Medicine (ABIM) made a major announcement regarding the discontinuation of the underlying board certification requirement. As Chair of the ABIM Pulmonary Disease Board, I am pleased to share this announcement, which was informed by feedback and guidance from a broad and diverse community and is evidence of ABIM's continued commitment to evolve the Maintenance of Certification (MOC) program into something that we all find meaningful and something in which all of us can take pride.

Through a new policy unanimously passed by the ABIM Council, ABIM announced that beginning January 1, 2016, diplomates certified in nine subspecialties of internal medicine will no longer need to maintain underlying certifications to stay certified. With this policy change, no disciplines in ABIM's MOC program will require maintenance of underlying certification in another discipline. All ABIM diplomates will be able to choose the certifications they wish to maintain.

This policy change is specific to MOC and does not affect the requirements for initial certification in Internal Medicine or subspecialties.

The policy removes requirements for maintenance of underlying certification in the following disciplines:

- Maintaining another certification will no longer be required to maintain certification in Adolescent Medicine, Hospice & Palliative Medicine, Sleep Medicine, and Sports Medicine.
- Maintaining Cardiovascular Disease certification will no longer be required to maintain certification in Advanced Heart Failure & Transplant Cardiology, Clinical Cardiac Electrophysiology, Interventional Cardiology, and Adult Congenital Heart Disease.
- Maintaining Gastroenterology certification will no longer be required to maintain certification in Transplant Hepatology.

Beginning January 1, 2016, diplomates certified in nine subspecialties of internal medicine will no longer need to maintain underlying certifications to stay certified.

Note: While the change to the underlying board certification requirement does not apply to maintaining a Pulmonary Disease or Critical Care Medicine certification, because neither currently requires or has previously required you to maintain another certification, it does apply to Sleep Medicine. Currently, if you maintain certification in Sleep Medicine, you also need to maintain certification in Internal Medicine or an ABIM subspecialty; however, after January 1, 2016, you will no longer need to maintain an underlying certification to stay certified in Sleep Medicine.

I encourage you to visit the Transforming ABIM blog (http://transforming.abim.org) to learn more about this change, as well as updates about ABIM's ongoing discussions with the internal medicine community and upcoming opportunities to provide input.

To learn more about your specific requirements and deadlines, or to check your certification status, log into www.abim.org to view your MOC Status Report.

I look forward to sharing more updates with you as we continue our work of ensuring the relevancy of MOC to pulmonary disease physicians across the country.

What if your PAH patient may not have PAH?

A ventilation-perfusion (V/Q) scan can rule out chronic thromboembolic pulmonary hypertension (CTEPH) in patients diagnosed with PAH, which is the only form of pulmonary hypertension that can be potentially cured by surgery.[1]

If you know what to look for, a V/Q scan makes it relatively easy to spot.[1]

1 in 25*

As many as **1 out of every 25** of your previously treated PE patients (>3 months of anticoagulation[2]) may develop CTEPH.[3,4*]

*Based on a study with 223 patients in which 3.8% were diagnosed with CTEPH within 2 years of their first episode of pulmonary embolism with or without prior deep-vein thrombosis (95% CI, 1.1 to 6.5). CTEPH did not develop after two years in any of the 132 remaining patients with more than 2 years of follow up.

VISIT **scan4CTEPH.COM** FOR MORE INFORMATION

References:

1. Kim NH, Delacroix M, Jenkins DP, et al. Chronic thromboembolic pulmonary hypertension. *J Am Coll Cardiol.* 2013;62(suppl D):D92-D99.

2. Wilkens H, Lang I, Behr J, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): updated recommendations of the Cologne Consensus Conference 2011. *Int J Cardiol.* 2011;154S:S54-S60.

3. Pengo V, Lensing AWA, Prins MH, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. *N Engl J Med.* 2004;350(22):2257-2264.

4. Tapson VF, Humbert M. Incidence and prevalence of chronic thromboembolic pulmonary hypertension: from acute to chronic pulmonary embolism. *Proc Am Thorac Soc.* 2006;3(7):564-567.

Bayer HealthCare LLC
100 Bayer Boulevard, Whippany, NJ 07981 USA

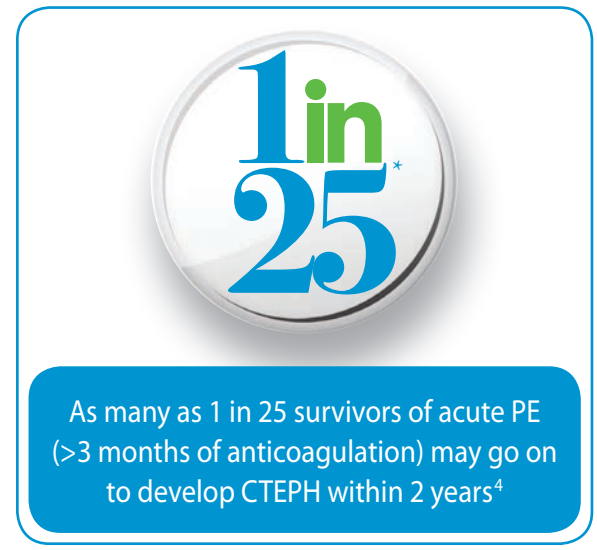
PP-400-US-1616 March 2015

Screening for CTEPH in Patients With Suspected Pulmonary Hypertension

presented by

RICHARD CHANNICK, MD

Richard N. Channick, MD, is Associate Professor of Medicine at Harvard Medical School, Boston, Massachusetts, and has been Director of the Pulmonary Hypertension and Thromboendarterectomy Program at Massachusetts General Hospital in Boston since 2009.



CTEPH IS A FORM OF PULMONARY HYPERTENSION

Chronic thromboembolic pulmonary hypertension is a form of pulmonary hypertension (PH), designated by the World Health Organization as Group 4 PH. There are 5 WHO Groups of PH[1]:

1: Pulmonary arterial hypertension

2: PH due to left heart disease

3: PH due to lung diseases and/or hypoxia

4: CTEPH

5: PH with unclear multifactorial mechanisms

Recently, Klok et al have coined the term "post-pulmonary embolism syndrome" to describe chronic complications of pulmonary embolism (PE), involving permanent changes in pulmonary artery flow, pulmonary gas exchange and/or cardiac function which are associated with symptoms of dyspnea and decreased exercise capacity.[2] The most serious manifestation of this syndrome—and the most serious complication of acute PE—is chronic thromboembolic pulmonary hypertension, or CTEPH.[2,3] As many as 1 in 25 survivors of acute PE may go on to develop CTEPH within 2 years.[4]

Hemodynamically, CTEPH is most often defined as a mean pulmonary arterial pressure (mPAP) ≥25 mmHg, with pulmonary capillary wedge pressure (PCWP) ≤15 mmHg. These levels must be obtained via right heart catheterization, and they must be observed in the presence of multiple chronic/organized, occlusive thrombi/emboli in the pulmonary arteries after at least 3 months of effective anticoagulation.[5]

Symptoms of CTEPH are nonspecific[6] and include dyspnea on exertion, fatigue, weakness, chest pain, syncope, hemoptysis, and lower-extremity edema.[7] Among the risk factors for CTEPH are unprovoked or recurrent PE, young age at the time of first PE, and splenectomy.[7]

CTEPH is unique among the five groups of PH insofar as it is the only form that is potentially curable—via pulmonary thromboendarterectomy (PTE, also known as pulmonary endarterectomy [PEA]), the treatment of choice for surgical candidates with CTEPH.[8-10] It is this potential to effect a curative treatment that makes it imperative to suspect and screen for CTEPH—and to differentiate CTEPH from other forms of PH—when patients present with symptoms consistent with PH.

HOW DOES CTEPH DEVELOP?

CTEPH results after a single PE or recurrent PEs that create endothelialized residua that obstruct or substantially narrow pulmonary arteries.[11] The absence or depletion of endogenous nitric oxide may contribute to endothelial dysfunction in CTEPH.[12] Obstruction and narrowing of the pulmonary arteries drives pulmonary arterial pressures to abnormal levels and increases pulmonary vascular resistance (PVR).[11] Over time, developing small vessel vasculopathy can lead to right ventricular afterload, progression of PH, and CTEPH.[13] If CTEPH is unrecognized or left untreated, right ventricular dysfunction can progress, ultimately resulting in right heart failure.[13]

HOW COMMON IS CTEPH?

Based on data from small observational studies that followed survivors of acute PE, incidence of CTEPH has been estimated to be 0.57% (N=866 survivors of acute PE observed) to 3.8% (N=314 survivors of acute PE observed)—or almost 1 in 25—within 2 years of the first acute event.[3,13] A more recent, but smaller (N=146 acute PE survivors followed for 26 months) study found that 8 survivors of acute PE were suspected to have CTEPH, and 7 of these—or 4.8% of the study population—were confirmed to have CTEPH.[14] Yet another study of survivors of acute PE (N=104) saw 5.8% of patients develop CTEPH within 2 years. Further follow-up saw an additional 4 cases develop beyond 2 years (time period not specified) for a total of 9.1% of the original study population.[15]

The absence of prior acute PE does not exclude a diagnosis of CTEPH[9,16,17]

Applying even the lower end of this range of estimates to the annual population of survivors of acute PE suggests there could be thousands of incident cases of CTEPH each year in the US. Further, though CTEPH is a complication of acute PE, as many as 25% to 30% of patients who have CTEPH may never have had an overt PE or a history suggestive of PE.[9,16,17] The true incidence of CTEPH may, therefore, be underestimated, because postembolism observational studies do not include patients who have no history of venous thromboembolism.[13]

HOW DO WE SCREEN FOR CTEPH?

As noted, symptoms of CTEPH are nonspecific, and as a result, CTEPH is often misdiagnosed and is under recognized in practice.[6] If after at least 3 months of anticoagulation following an episode of acute PE a patient still has or develops symptoms of dyspnea, fatigue, decreased exercise capacity, or another of the symptoms of PH, one should suspect and either screen for CTEPH or refer the patient to a PH specialist who can perform CTEPH screening.[18,19]
As noted above, as many as 30% of patients who are ultimately diagnosed with CTEPH may have no history of overt acute PE, so any patient who has unexplained dyspnea should also be screened for CTEPH.[9, 16,17]

If after 3 months of anticoagulation following an episode of acute PE a patient still has or develops such symptoms, CTEPH should be suspected and the patient referred to a PH specialist who can perform CTEPH screening[17]

Computed tomographic pulmonary angiography (CTPA) has become the standard diagnostic test for acute PE, and a good-quality CTPA that is negative for acute PE effectively rules the diagnosis out.[19] Unlike for acute PE, though, CTPA is not a preferred diagnostic test for CTEPH.[8] Instead, the ventilation/perfusion, or V/Q, scan is the preferred and recommended screening test for CTEPH.[8] Tunariu et al demonstrated that as a screening test for CTEPH, the V/Q scan had >96% sensitivity, meaning that a negative (ie, normal) V/Q scan essentially rules out the presence of CTEPH.[20] Conversely, Tunariu et al also showed that CTPA had a sensitivity of only 51% as a screening test for CTEPH, with a falsely negative finding in 38 of 78 cases studied.[20] Multiple national and international guidelines recommend the use of the V/Q scan as the CTEPH screening tool of choice.[5,8,21-23] Though it can detect chronic thromboembolic disease in segmental, lobar, or main pulmonary arteries, CTPA may miss disease that is

confined to very distal segmental or subsegmental pulmonary arteries.[8,24]

The V/Q scan has many attributes that contribute to its utility as a screening tool for CTEPH.[8] It is easy to read—suspected perfusion defects, regardless of origin, are readily recognizable. V/Q scanning also requires less radiation exposure than CTPA, and it avoids complications from administration of IV contrast. Finally, it offers a lower likelihood of incidental findings.

> PTE surgery is the first-line treatment of choice for surgical candidates who have CTEPH[15]

Many patients who have been diagnosed with pulmonary arterial hypertension (PAH) have never had a V/Q scan to rule out potentially curable CTEPH. Findings from the Pulmonary Arterial Hypertension-Quality Enhancement Research Initiative (PAH-QuERI, N=786) demonstrated that 43% of patients who had been diagnosed with PAH had been so diagnosed despite never having received a V/Q scan to screen for, and potentially rule out, CTEPH.[25] This finding suggests that patients who have been previously diagnosed with PAH without having had a V/Q scan and who are not meeting their PAH treatment goals should receive a V/Q scan to screen for CTEPH.

To stress the importance of the V/Q scan as a screening tool for CTEPH, the World Symposium on Pulmonary Hypertension observed that "underutilization of V/Q scans in screening PH invites potential misdiagnosis of PAH."[8] Such misdiagnosis can result in delay of assessment for potentially curative surgery for CTEPH.[6,26] If V/Q scanning is not readily available, the patient should be referred to a center that can perform a V/Q scan.

CONFIRMATION OF CTEPH DIAGNOSIS

An abnormal V/Q scan showing perfusion defects is not enough on its own to diagnose CTEPH. To confirm CTEPH, right heart catheterization (RHC) must be performed to confirm mean PAP ≥25 mmHg, with pulmonary capillary wedge pressure (PCWP) ≤15 mmHg. Selective pulmonary angiography is typically used to confirm presence of CTEPH lesions.[8] CTPA and magnetic resonance angiography can contribute complementary information on the lesions, their surroundings, and their accessibility.[5,8]

Once the diagnosis of CTEPH is confirmed, all CTEPH patients must be assessed for operability by an experienced CTEPH team that would plan, perform, and follow-up the patient's surgery. Operability assessment must consider the patient's risk, including quality of and accessibility of lesions, hemodynamic assessment, and consideration of comorbidities and patient characteristics.[8] If one experienced CTEPH team determines that a patient has inoperable disease, a corroborating opinion from a second experienced CTEPH team should be secured, if possible.[8] This is because operability assessment is subjective, and what may be deemed by one CTEPH team as inoperable disease may well be deemed operable by another experienced CTEPH team.

CTEPH TREATMENT IN SURGICAL CANDIDATES: PULMONARY THROMBOENDARTERECTOMY

Referral of CTEPH patients to PH centers for confirmation of diagnosis, operability assessment, and comprehensive care is essential.[5] Because it is potentially curative, PTE surgery is considered the first-line treatment of choice for patients diagnosed with CTEPH who are appropriate surgical candidates.[8-10] Rather than reserving PTE surgery as a "last-ditch" treatment option, patients who have operable CTEPH should be referred for surgery without delay.[8] Though all CTEPH patients require lifelong anticoagulation to prevent in situ pulmonary artery thrombosis and recurrent venous thromboembolism,[8] anticoagulation is not sufficient to treat the progressive right ventricular dysfunction that results from CTEPH. PTE surgery allows for the removal of central obstructing lesions, resulting in improvement and often normalization of pulmonary hemodynamics.[7] About two-thirds of patients have normal hemodynamics following PTE.[27]

REFERENCES

1. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol.* 2013;62(25 suppl):D34-D41.
2. Klok FA, van der Hulle T, den Exter PL, et al. The post-PE syndrome: a new concept for chronic complications of pulmonary embolism. *Blood Rev.* 2014;28(6):221-226.
3. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics—2014 update: A report from the American Heart Association. *Circulation.* 2014;129(3):e28-e292.
4. Pengo V, Lensing AWA, Prins MH, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. *N Engl J Med.* 2004;350(22):2257-2264.
5. Wilkens H, Lang I, Behr J, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): updated recommendations of the Cologne Consensus Conference 2011. *Int J Cardiol.* 2011;154S:S54-S60.
6. Tapson VF, Humbert M. Incidence and prevalence of chronic thromboembolic pulmonary hypertension: from acute to chronic pulmonary embolism. *Proc Am Thorac Soc.* 2006;3(7):564-567.
7. Piazza G, Goldhaber SZ. Chronic thromboembolic pulmonary hypertension. *N Engl J Med.* 2011;364(4):351-360.
8. Kim NH, Delcroix M, Jenkins DP, et al. Chronic thromboembolic pulmonary hypertension. *J Am Coll Cardiol.* 2013;62(suppl D):D92-D99.
9. Jamieson SW, Kapelanski DP, Sakakibara N, et al. Pulmonary endarterectomy: experience and lessons learned in 1500 cases. *Ann Thorac Surg.* 2003;76(5):1457-1464.
10. Keogh AM, Mayer E, Benza RL, et al. Interventional and surgical modalities of treatment in pulmonary hypertension. *J Am Coll Cardiol.* 2009;54(suppl 1):S67-S77.
11. Humbert M. Pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: pathophysiology. *Eur Respir Rev.* 2010;19(115):59-63.
12. Skoro-Sajer N, Mittermayer F, Panzenboeck A, et al. Asymmetric dimethylarginine is increased in chronic thromboembolic pulmonary hypertension. *Am J Respir Crit Care Med.* 2007;176(11):1154-1160.
13. Fedullo P, Kerr KM, Kim NH, Auger WR. Chronic thromboembolic pulmonary hypertension. *Am J Respir Crit Care Med.* 2011;183(12):1605-1613.
14. Guérin L, Couturaud F, Parent F, et al. Prevalence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. Prevalence of CTEPH after pulmonary embolism. *Thromb Haemost.* 2014;112(3):598-605.
15. Martí D, Gómez V, Escobar C et al. Incidence of symptomatic and asymptomatic chronic thromboembolic pulmonary hypertension. *Arch Bronconeumol.* 2010;46(12):628-633.
16. Pepke-Zaba J, Delcroix M, Lang I, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. *Circulation.* 2011;124(18):1973-1981.
17. Bonderman D, Wilkens H, Wakounig H-J, et al. Risk factors for chronic thromboembolic pulmonary hypertension. *Eur Respir J.* 2009;33(2):325-331.
18. McLaughlin VV, Archer SL, Badesch BD, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension. A report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association. Developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. *Circulation.* 2009;119(16):2250-2294.
19. Tapson VF. Advances in the diagnosis and treatment of acute pulmonary embolism. *F1000 Reports Med.* 2012;4:9.
20. Tunariu N, Gibbs SJR, Win Z, et al. Ventilation–perfusion scintigraphy is more sensitive than multidetector CTPA in detecting chronic thromboembolic pulmonary disease as a treatable cause of pulmonary hypertension. *J Nucl Med* 2007;48(5):680-684.
21. Galiè N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J.* 2009;30(20):2493-2537.
22. Jaff MR, McMurtry S, Archer SI, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: A scientific statement from the American Heart Association. *Circulation.* 2011;123(16):1788-1830.
23. Mehta S, Helmersen D, Provencher S, et al. Diagnostic evaluation and management of chronic thromboembolic pulmonary hypertension: a clinical practice guideline. *Can Respir J.* 2010;17(6):301-334.
24. Sugiura T, Tanabe N, Matsuura Y, et al. Role of 320-slice CT imaging in the diagnostic workup of patients with chronic thromboembolic pulmonary hypertension. *Chest.* 2013;143(4):1070-1077.
25. McLaughlin VV, Langer A, Tan M, et al. Contemporary trends in the diagnosis and management of pulmonary arterial hypertension: An initiative to close the care gap. *Chest*. 2013;143(2):324-332.
26. Kim NH, Lang IM. Risk factors for chronic thromboembolic pulmonary hypertension. *Eur Respir Rev.* 2012;21(123):27-31.
27. Freed DH, Thomson BM, Berman M, et al. Survival after pulmonary thromboendarterectomy: effect of residual pulmonary hypertension. *J Thorac Cardiovasc Surg.* 2011;141(2):383-387.

*Based on a study with 223 patients in which 3.8% were diagnosed with CTEPH within 2 years of their first episode of pulmonary embolism with or without prior deep-vein thrombosis (95% CI, 1.1 to 6.5).[4]

VISIT
scan4CTEPH.com
FOR MORE INFORMATION

Bayer HealthCare LLC
100 Bayer Boulevard, Whippany, NJ 07981 USA

PP-400-US-1575 March 2015

Getting to know our incoming CHEST President

Dr. Barbara A. Phillips, MSPH, FCCP, will be welcomed as CHEST's new President during the CHEST Annual Meeting 2015 in Montréal next month. She is a Professor of Pulmonary, Critical Care, and Sleep Medicine in the Department of Internal Medicine and Medical Director, Sleep Laboratory at the University of Kentucky College of Medicine. She is board-certified in internal medicine, pulmonary medicine, and sleep medicine. After joining CHEST as an affiliate member in 1982, Dr. Phillips advanced to Fellow in 1983. She became a member of the Sleep Medicine NetWork and a CHEST Governor for Kentucky. She has chaired the Sleep Institute and is Deputy Editor, SEEK Editorial Board Sleep Medicine (Second and Third Editions). Dr. Phillips chaired the National Sleep Foundation and has served on the Boards of the American Lung Association, the American Academy of Sleep Medicine, and the American Board of Sleep Medicine. Dr. Phillips received a Sleep Academic Award from the National Institutes of Health and was presented with the College Medalist Award at CHEST 2013. Dr. Phillips' research interests are effects of sleep apnea on performance and outcomes, genetic risk factors for sleep apnea, nonpharmacologic treatment of sleep apnea, and sleep in aging.

I'd like to help the organization continue its remarkable growth and modernization. I just want to make sure we stay on course, ensure further diversification of our staff and membership, and continue to fulfill our ambitious mission.

We asked Dr. Phillips for some thoughts on her upcoming CHEST presidency.

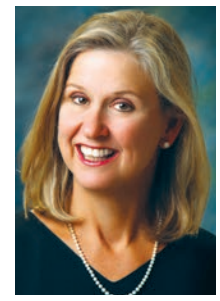
1. What would you like to accomplish as President of CHEST?
I'd like to help the organization continue its remarkable growth and modernization. In the past few years, we have expanded our mission and membership, built new headquarters, developed an empowered and effective Board, launched a new take on global meetings with CHEST World Congress (come to Shanghai in April!), brought our technology infrastructure up to speed, undergone a rebranding process, and seen remarkable growth in the strength of our journal. That's a lot! I personally don't have any great new projects planned beyond what we've outlined in our strategic plan that runs through 2017; I just want to make sure we stay on course, ensure further diversification of our staff and membership, and continue to fulfill our ambitious mission.

2. What do you consider to be the greatest strength of CHEST, and how will you build upon this during your Presidency?
Our greatest strength lies with our talented human resources, both members and staff, who are committing to ensuring that CHEST remains the global (or as I like to say, "intergalactic") leader in pulmonary, critical care, and sleep medicine education.

3. What are some challenges facing CHEST, and how will you address these challenges?
Communication, capacity, and competition.

CHEST is a large organization with many moving parts, and excellent, timely communication between our leaders, members, and staff is an important challenge for us.

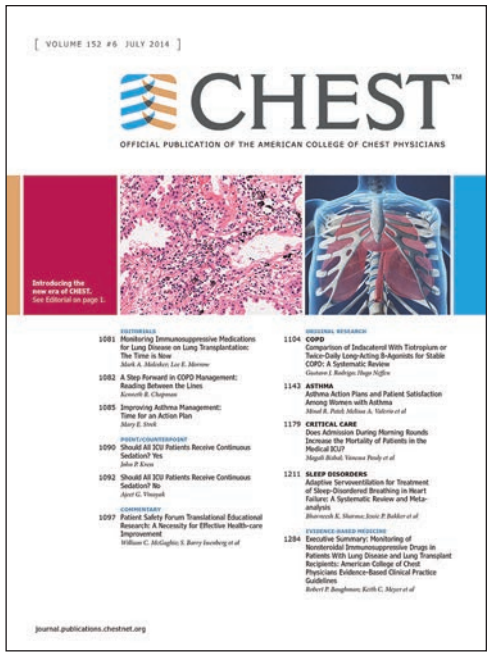
In order to achieve our mission, "To champion the prevention, diagnosis, and treatment of chest diseases through education, communication, and research," we need boots on the ground. CHEST is working to build capacity among both membership and staff to take us to the next level.


DR. PHILLIPS

Competition for members is also a significant challenge for CHEST and for medical organizations in general. For example, in the 1950s, about 75% of US physicians were American Medical Association (AMA) members. That percentage has steadily decreased over the years, to about 15% today. At CHEST, we're pleased to be able to say that we have 85% of US physicians specializing in pulmonary and critical care as members, plus nearly 50% of those in sleep medicine and pediatric pulmonology. But there is no cause for complacency. Busy professionals will only join organizations that are relevant and helpful to their lives. CHEST strives to meet that challenge.

4. And finally, what is your charge to the members and new Fellows of CHEST?
First, WELCOME! Second, please get involved. Join a NetWork (or two). Connect with other members through the e-Community. Attend the annual meeting. Submit your research and case reports. Organize a session submission. Volunteer for a committee. And please come meet us. We want to know you!

This month in *CHEST*: Editor's picks



BY DR. RICHARD S. IRWIN, MASTER FCCP

Tobacco Smoke Exposure, Airway Resistance, and Asthma in School-age Children: The Generation R Study. *By Dr. H. den Dekker et al.*

Silicosis Appears Inevitable Among Former Denim Sandblasters: A 4-Year Follow-up Study. *By Dr. M. Akgun et al.*

Clinical Worsening as Composite Study End Point in Pediatric Pulmonary Arterial Hypertension. *By Dr. M-J Ploegstra et al.*

POINT AND COUNTERPOINT
Does the Risk of Electronic Cigarettes Exceed Potential Benefits?
Yes: *Dr. M. V. Avdalovic and Dr. S. Murin.*
No: *Dr. H. R. Middlekauff.*
Rebuttals *by Drs. Avdalovic, Murin, and Middlekauff.*

AHEAD OF THE CURVE
Cannabis Smoking in 2015: A Concern for Lung Health?
By Dr. J. R. Biehl and Dr. E. L. Burnham.

MEDICAL ETHICS
Ebola Virus Disease: Ethics and Emergency Medical Response Policy. *By Dr. N. S. Jecker et al.*

GIANTS IN CHEST MEDICINE
Highlighting Dr. John (Jack) G. Weg, Master FCCP
By Dr. R. S. Irwin, and Ms. P. Goorsky.

In Memoriam

Dr. Christopher D. Spradley, FCCP, died July 17, 2015.

Dr. Spradley was a member of the Critical Care NetWork and also served as a moderator for the CHEST e-Community. He served as the director of the Medical Intensive Care Unit at Scott & White Hospital in Temple, Texas, and was also director of the hospital's Pulmonary Hypertension Center.

Dr. Spradley attended Texas A&M University System Health Science Center College of Medicine to earn his Doctor of Medicine, and after a residency in internal medicine at Scott & White Hospital, he became a fellow in Pulmonary, Critical Care, and Sleep Medicine at Scott & White.

He specialized in critical care medicine, PAH, diseases of the chest, sleep disorders, and palliative care.

Our condolences go out to the Spradley family and friends.

CHEST 2015: Cutting-edge education, Montréal neighborhoods with authentic cuisine

When you travel to Montréal to attend the CHEST Annual Meeting 2015, October 24 to 28, you don't want to miss a minute of the cutting-edge education sessions and simulation training—but you also won't want to ignore the great city where you will be staying. Knowing that your time may be limited, we came up with a list of restaurants near the convention center and local neighborhoods that you can explore within the short breaks in your schedule.

Enjoy a walk or grab a cab to enjoy these nearby eats:

• Pho Bang New York (3-minute walk): this casual restaurant offers Vietnamese soups and buns.

• Olive & Gourmando (6-minute walk): you'll enjoy creative sandwiches, local beer and wine selections, and pastries galore!

• March 27 (11-minute walk): this French bistro serves small plates and is known for its tartare.

• Mai Xiang Yuan (5-minute walk): located in Chinatown, this restaurant serves up delicious dumplings and authentic Chinese cuisine.

CHRIS DLUGOSZ/FLICKR/CC BY 2.0

Looking for a quick excursion during a break in your education schedule? These nearby neighborhoods will offer you a glimpse into Montréal:

• Visit Old Montréal, located only a few minutes walk from the convention center. Old Montréal offers a glimpse into Montréal's history blended with hip, urban hotspots. Complete with cobblestone paths, chic art galleries, 19th century architecture, and trendy boutiques, this neighborhood will keep you busy during your spare time. Learn more about Old Montréal from our earlier article published in the April edition of *CHEST Physician*.

• Visit Chinatown. Also located minutes away from the convention center, this neighborhood is filled with Asian restaurants, food markets, and convenience stores.

We know you'll enjoy Montréal and CHEST 2015's extensive educational offerings. You'll receive relevant updates on patient care, and practice management strategies will offer insight, perspective, and inspiration you can seamlessly incorporate into your practice to stay at the forefront of clinical chest medicine.

Begin planning your trip to Montréal now with help from Montréal's tourism website, www.tourisme-montreal.org. Start planning your learning itinerary with the CHEST 2015 mobile-ready website or apps for iOS or Android. Find links to the mobile-ready website and apps, and learn more about CHEST 2015 at chestmeeting.chestnet.org.

FROM THE EVP/CEO: Cultivating future leaders

At CHEST, cultivating future leaders in chest medicine is of paramount importance to us. Our members who desire to become leaders are prepared to advance our goals and initiatives, as well as become leaders within their own communities and institutions. That's why we work to inspire, train, mentor, and galvanize new leaders.

When looking for leaders, volunteers, and faculty for CHEST, we most often draw from our own CHEST community—identifying members interested in engaging with us to help build the future of our organization and advance chest medicine. Knowing each person's path to leadership is different, we have undertaken a new initiative, CHEST Academies, to help identify and provide essential training and development for future leaders.


MR. MARKOWSKI

Over the past several years, the Leadership Development Task Force supported these efforts by launching a mentorship program, an annual leadership development course, and a standard approach to preparing leaders and volunteers for their role in the organization. Our new Academies Work Group, following on the successes of the Leadership Development Task Force, will carry this work forward and further develop training opportunities in education, faculty training, guideline development, and leadership. The work group initially will focus on two distinct tracks: faculty development and leadership development.

CHEST Annual Meeting 2015 will mark the launch of our first course tracks being offered as part of the new CHEST Academies. These tracks are direct pathways to the latest training for leaders in health care and for faculty in chest medicine.

The work group has made fast progress, and I'm happy to share that CHEST Annual Meeting 2015 will mark the launch of our first course tracks being offered as part of the new CHEST Academies. These tracks are direct pathways to the latest training for leaders in health care and for faculty in chest medicine. Core competencies to be included in the tracks include:

- Leadership—personal characteristics, communication, teamwork, finance, and strategic planning
- Faculty—educational goals and objectives, gap analysis and needs assessment, point of care and large group teaching, and instructional methods

I want to personally thank our current and past CHEST leadership for their contributions toward our success, the Academies Work Group for moving this opportunity forward, and those pioneers who will participate in our first CHEST Academies offerings at CHEST 2015.

This is only the beginning. Because we value our leaders and want to help them to succeed personally and professionally, we're committed to continuing to develop and offer year-round opportunities for leadership and faculty development. Members also can access additional resources for leadership development in the Get Involved section on chestnet.org.

When looking for leaders, volunteers, and faculty for CHEST, we most often draw from our own CHEST community. We have undertaken a new initiative, CHEST Academies, to help identify and provide essential training and development for future leaders.

I welcome your input on how we can continue to advance professional development within our CHEST community. As always, feel free to connect with me to share your ideas. I invite you to follow me on Twitter, @PMarkowskiACCP, or look for me at CHEST 2015, October 24-28, in Montréal.

NAMDRC tackles archaic Medicare rules

BY PHIL PORTE
NAMDRC Executive Director

Under current Medicare law and regulations, the Centers for Medicare and Medicaid Services (CMS) has a confusing mix of rules that is complicated to understand and certainly contrary to the current standards of practice. Earlier this year, NAMDRC, CHEST, and about a dozen other societies wrote to CMS citing problems:


MR. PORTE

• Medicare does not recognize FDA classifications of devices as ventilators. Therefore, while one agency within the US Department of Health & Human Services is specifically charged with the responsibility for determining safety and efficacy of medical devices and providing strict rules for labeling, a sister agency in the same department is not bound to accept those determinations. This has the effect of CMS stating that "just because FDA calls a device a ventilator does not make it a ventilator."

This bizarre scenario is undoubtedly tied to a current statute that requires CMS to pay for certain ventilators under the "frequent and substantial servicing" payment methodology rather than the "capped rental" payment methodology. If CMS believes it might pay too much for home mechanical ventilators, it simply says that the worrisome device is actually a "respiratory assist device," a term it has created for payment purposes.

• In 2001, CMS issued a Decision Memo that has the effect of signaling that in order to receive home mechanical ventilation, there must be the presence of an artificial airway AND removal of the device would lead to death. This principle is fraught with problems from various perspectives. First, even though the memo explicitly states "contractor discretion," the key Medicare contractors have repeatedly signaled they have no flexibility and must adhere to that principle.

Secondly, with the advent of noninvasive mechanical ventilation, CMS created codes for processing such devices through the payment system, even though the 2001 Decision Memo refers to the need for an artificial airway. The inconsistency in these policies has led to confusion from ordering physicians and suppliers, as well.

• Now, in 2015, the state-of-the-art of home mechanical ventilation is a world apart from 2001, and no policies have been updated related to home mechanical ventilation. Respiratory assist devices (RADs) or bilevel devices to everyone except Medicare recipients, are part of the problem. Because access to RADs are covered by very strict, inflexible Medicare rules, physicians and suppliers often find it easier to prescribe a ventilator for treatment of respiratory failure.

Possible solutions: Crafting solutions might seem relatively easy, but we want to ensure that rules we might agree to today need to be flexible enough to address innovations 2, 3, or 5 years from now. Therefore, the pathway of a national coverage determination (NCD) might not be the best approach because once an NCD is set into policy, it is a challenging effort to modify it, even if CMS agrees that problems with the relatively new policy need adjustment. Therefore, NAMDRC is working with other societies to craft some important principles and shape those principles into new policies that CMS could adopt outside of the NCD framework. Those principles include the following:

• A specific definition of "respiratory failure" that can be used to guide physicians, suppliers, and payers. Under this principle, if a diagnosis of respiratory failure meets the clinical definition and the physician certifies the medical necessity of treating respiratory failure, part of the treatment plan, by definition, includes a home mechanical ventilator.

• We see little need to distinguish between invasive and noninvasive home mechanical ventilation for coverage purposes. The principle outlined in the 2001 Decision Memo is outdated, and no one genuinely believes that, by definition, the most critically ill must have a trach in order to survive. Let the physician determine the best approach; and in the case of many patients, particularly in the neuromuscular arena, a patient might use invasive mechanical ventilation nocturnally and noninvasive ventilation at other times. Importantly, most devices today can accommodate either approach.

We want to ensure that rules we might agree to today need to be flexible enough to address innovations 2, 3, or 5 years from now. NAMDRC is working with other societies to craft some important principles and shape those principles into new policies that CMS could adopt outside of the NCD framework.

• CMS's RAD policy should be reshaped to provide greater flexibility to ensure that bilevel devices are available to those patients where less intensive therapy is appropriate.

We are hopeful that a revamped set of policies could be in place by the end of the year or early in 2016.

CHEST Fellow, Dr. Jack A. Roth, receives ASTRO honor

The American Society for Radiation Oncology (ASTRO) has selected leading surgeon and researcher Dr. Jack A. Roth, FCCP, as the 2015 Honorary Member, the highest honor ASTRO bestows on distinguished cancer researchers, scientists, and leaders in disciplines other than radiation oncology, radiobiology, or radiation physics. Dr. Roth will be inducted as the 2015 ASTRO Honorary Member during the Awards Ceremony in October, at ASTRO's 57th Annual Meeting, in San Antonio.


DR. ROTH

Dr. Roth is professor, Department of Thoracic and Cardiovascular Surgery, Division of Surgery, at MD Anderson Cancer Center, Houston, and chief, Section of Thoracic Molecular Oncology, Department of Thoracic and Cardiovascular Surgery, Division of Surgery, MD Anderson.

He cited his and colleagues' study "Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomized trials," published in Lancet Oncology in May 2015, as his most recent career highlight. Dr. Roth was an early innovator in the development of gene therapy for cancer, and led the first tumor suppressor gene therapy clinical trials approved by the National Institutes of Health Recombinant DNA Advisory Committee and the US Food and Drug Administration. His work was the first gene therapy in cancer approved for human use.

Join colleagues on the Donor Wall of Honor

With CHEST 2015 quickly approaching, do not miss the opportunity to join your colleagues being recognized on the popular and highly visible **Donor Wall of Honor**. The wall is more than just a listing of donor names; it is a way you can show other members that you made a commitment to strengthen your foundation.

As an Annual Fund Giving Club member, you will enjoy a great number of recognition benefits, including access to a special donor lounge at the meeting; recognition for supporting the foundation in CHEST and CHEST Foundation publications, on our website, and on the Donor Wall of Honor; as well as receipt of a foundation donor pin, ribbon, and a special gift.

Thank you for helping lead this organization in so many ways, and we would be grateful to have your philanthropic support of the CHEST Foundation.

To continue to foster a culture of giving, please visit www.chestnet.org/donate to make your online gift, or fill out and mail the donor envelope that is inside your summer edition of the *Donor Spotlight*.

NETWORKS: Measles, air quality, end of life, high-flow nasal O_2, sleep curriculum project

Disaster Response

The respiratory transmission of measles: global concern

A record number of measles cases during 2014 were reported from CDC's National Center for Immunization and Respiratory Diseases (NCIRD). The majority of these cases involved unvaccinated persons. The measles virus type (B3) was identical to the outbreak in the Philippines in 2014. Worldwide, approximately 20 million measles cases occur annually. In 2013, there were 145,700 deaths globally, and in 1980, measles caused 2.6 million deaths annually. Accelerated immunization activities have had an impact on reducing deaths. Measles vaccination prevented an estimated 15.6 million deaths, and global measles deaths have decreased by 75%.

Outbreaks can be deadly in countries experiencing or recovering from a natural disaster or conflict. Damage to health infrastructure and health services interrupts routine immunization, and overcrowding in residential camps greatly increases the risk of infection. Everyone for whom MMR (measles-mumps-rubella) is recommended should be vaccinated. This protects people who cannot receive MMR vaccine, and those who might have serious complications from measles. Keeping vaccination rates high is critical for preventing measles from spreading.


MR. ROTH

Measles can spread through coughing and sneezing. The virus can live for up to 2 hours on a surface or in an airspace where the infected person coughed or sneezed. If people breathe the contaminated air or touch an infected surface and then touch their eyes, noses, or mouths, they can become infected. If one person has it, 90% of the people close to that person who are not immune will also become infected. Measles can spread from 4 days before to 4 days after the rash appears. Children younger than 5 years of age and adults older than 20 years of age are more likely to have complications.

References:
CDC. MMWR Morb Mortal Wkly Rep. 2015;64(14):373.
WHO Fact Sheet on Measles (2014). WHO.int. Accessed July 5, 2015.
CDC Fact Sheet Measles. cdc.gov. Accessed July 5, 2015.

Alan Roth, RRT, MS, MBA
Steering Committee Member

Occupational and Environmental Health

Air quality index and global health: hold your breath

An air quality index (AQI) is a numerical method for national agencies to inform the public on the degree of current air pollution and to predict future pollution trends. As AQI increases, more people are likely to experience adverse health effects. For example, Canada uses Air Quality Health Index (airhealth.ca) and Singapore uses the Pollutant Standards Index (haze.gov.sg). Parameters measured include ground level ozone, particulates, carbon monoxide, sulphur dioxide, and nitrogen dioxide. The concentration of these pollutants is translated into a public health advisory, which may be color coded or numerical. The message, which targets vulnerable populations and the general public, may declare an action day to avoid exposure and to make recommendations about public transportation. These measurements are usually made at specific air monitoring stations, such as United States


DR. HARANATH

Continued on following page

Continued from previous page

embassies. Information from various global agencies is displayed at http://waqi.info. Adverse health effects are typically estimated based on epidemiological studies. The United States Environmental Protection Agency has created standards and guidelines, which have been adopted and used globally (airnow.gov). It is, however, surprising that many American cities have worse air quality levels than many developing countries. Clearly there is much work to be done. Outdoor and household air pollution is a serious threat to health and the environment. The Occupational and Environmental Health NetWork is committed to promoting global lung health. At CHEST 2015, join us for our NetWork Featured Lecture on October 26 at 7:30 am. See you in Montréal. Au revoir!

Dr. Sai Praveen Haranath, FCCP
Steering Committee Member

Palliative and End-of-Life Care

Futility and interventions at the end of life

Futility in medicine is an ancient concept with implications for the modern world.

In a medical context, *futility* implies that in the setting of serious life-threatening illness, there is an agreed-upon goal, a course of treatment aimed at achieving this goal, and a virtual certainty that the action will fail to achieve it (Trotter. *Camb Q Healthc Ethics*. 1999;8[4]:527). What is challenging to the medical community, as well as society at large, is the setting of those goals using evidence-based therapies and the representation to the patient and family of these and all other options, using the community standards of care combined with the best interest of the patient to help solve end-of-life dilemmas (Weijer. *West J Med*. 1999;170[5]:254).


DR. CALVES

In the patient who is clearly at the end of life with no reasonable hope for cure and who understands the implications of his or her prognosis, there must be a refocus of aggressive care toward smaller and more intimate and, thus, more achievable goals.

Relief of pain, alleviation of dyspnea, control of nausea and vomiting, as well as the simple act of being present to the patient and family are hallmarks of truly humane interventions at the end of life.

When distilled to its purest form, any intervention that seeks to alleviate patients' suffering and helps them achieve their goal, be it a chest tube, diverting colostomy, intravenous morphine drip, or holding their hand, fulfills the obligation to respect the life with which we are entrusted.

Dr. Pedro Calves, FCCP
Steering Committee Member

Respiratory Care

High-flow nasal oxygen therapy: new insights to efficacy and mechanisms of action

High-flow nasal oxygen therapy (HFNO) is now commonly used in ICUs worldwide. So far, in 2015, there are at least 13 publications retrieved when searching PubMed for "high flow oxygen" in the title. In this brief review, HFNO will refer only to heated humidified oxygen therapy provided by nasal cannula at flows from 30 to 50 L/min.

The application of HFNO fairly consistently improves oxygenation over high-flow face mask or Venturi mask devices (Parke et al. *Respir Care*. 2011;56[3]:265; Maggiore et al. *Am J Respir Crit Care Med*. 2014;190[3]:282). Two recent studies suggest that the use of HFNO in patients with hypoxemic respiratory failure may be at least as efficacious as NIPPV. Frat and colleagues assigned 310 hypoxemic patients (P/F ≤300 on 10 L nasal cannula) in a medical-surgical ICU to standard nasal cannula, HFNO, or noninvasive positive pressure ventilation (NIPPV).


DR. BOWTON

There were significantly more ventilator-free days and lower 28-day mortality in the HFNO group (Frat et al. *N Engl J Med*. 2015;372[23]:2177). HFNO was noninferior to NIPPV in a randomized study of 830 cardiothoracic surgery patients at high risk for respiratory failure after extubation (Stephan et al. *JAMA*. 2015;213[23]:2331).

In addition to its efficacy, HFNO appears more comfortable for patients than NIPPV (Frat et al. Respir Care. 2015;60[2]:170) and less likely to cause facial skin breakdown (Stephan et al. *JAMA*. 2015;213[23]:2331).

The successful application of HFNO to prevent hypoxemia in patients undergoing endotracheal intubation has also been reported (Miguel-Montanes et al. *Crit Care Med*. 2015;43[3]:574). The mechanisms by which HFNO results in improved oxygenation and comfort for patients have not been completely elucidated but include the generation of CPAP (Parke et al. *Respir Care*. 2011;56[3]:265), potentially countering the impact of intrinsic PEEP on work of breathing as well as increasing functional residual capacity and washing out dead space (Spoletini et al. *CHEST*. 2015;148[1]:253). Whether the amount of CPAP generated (generally only 2 to 3 cm H_2O) is sufficient to account for these effects is unclear but will be a fruitful field for further study.

Dr. David Bowton, FCCP
Steering Committee Vice-Chair

Sleep Medicine

Sleep Medicine NetWork update fall 2015

It's been a busy year for the CHEST Sleep Medicine NetWork. Due to the hard work of our NetWork and steering committee members, we have accomplished several achievements that should benefit all of the CHEST membership. Some of the network's accomplishments and highlights include:

• CHEST SEEK Sleep Medicine: 4th Edition was published in August.

• The 2015 Sleep Medicine Board Review course was held in Washington, DC.

• The Sleep Curriculum Project, chaired by Dr. David Schulman, MPH, FCCP, includes the development of a set of curricular milestones and entrustable professional activities on clinically relevant sleep medicine topics and competencies that should be taught to all pulmonary fellows during their training.

• Several members of the network have been developing educational materials for patients and the general public as part of a larger collaborative project between the CHEST Foundation and the American Lung Association.

• The NetWork Steering Committee has provided input and opinions to several national societies, including the National Sleep Foundation (NSF) and American Academy of Sleep Medicine, on upcoming and recently published policies and professional statements.

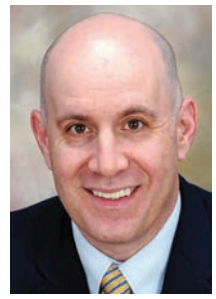
• Dr. Barbara Phillips, MSPH, FCCP, has been appointed as the CHEST representative to the NSF Drowsy Driving Consensus Work Group. The work group's objective is to refine the drowsy driving threshold definition for the purpose of public policy.

• Several of our NetWork members

Two recent studies suggest that the use of HFNO in patients with hypoxemic respiratory failure may be at least as efficacious as NIPPV.

were involved with developing questions for CHEST Challenge at the upcoming CHEST 2015 annual meeting. Good luck fellows with these questions!

The Sleep Medicine NetWork has been busy developing a strong educational curriculum that will be presented at the upcoming CHEST 2015 Annual Meeting in Montréal. In addition to our Sleep Medicine 2015: Year in Review and Clinical Update postgraduate course, there will be over 20 additional sessions covering the spectrum of sleep-related topics. Many of these sessions will be presented in collaboration with members from the Canadian Thoracic Society. Several sessions will also cover the recent SERVE-HF data related to adaptive-servo ventilation (ASV) for patients with central sleep apnea and congestive heart failure.


DR. FREEDMAN

Also during CHEST 2015, we have changed the format for our network business meeting, which will be held on Monday, October 26, at 4:30 pm. This year's meeting will be exclusively devoted to gathering input from our membership to ensure that our 2016 strategic plan addresses the educational needs of all of our members. We hope to see you there.

Finally, the NetWork Steering Committee will be welcoming four new members, including a physician in training. We would like to thank our departing steering committee members Lee Brooks, Chris Frey, and Paul Selecky for all of their hard work and dedication.

See you in Montréal.

Dr. Neil Freedman, FCCP
Chair

CLASSIFIEDS

Also available at MedJobNetwork.com

PROFESSIONAL OPPORTUNITIES

Pulmonology Opportunity
Sequim / Port Angeles, Washington

Come join us on the Olympic Peninsula in Washington State in the communities of Sequim and Port Angeles located between the Strait of Juan de Fuca and the Olympic Mountains. We are looking for a well trained BC/BE pulmonary and critical care specialist who is highly motivated and team orientated. We are a multispecialty group currently including two pulmonologists servicing a large referral area. The position will combine outpatient and inpatient pulmonary medicine. There are no Sleep Medicine responsibilities. Call and hospital coverage is shared with an outstanding hospitalist service; the position has minimal night time call responsibilities.

Nestled on the Olympic Peninsula just 70 miles northwest of Seattle, Sequim and Port Angeles have less rainfall than Seattle, virtually no commuter traffic, and provide access to abundant outdoor recreation, a wide range of community events and attractions, and easy access to Seattle and Victoria, B.C. With Olympic National Park (a world heritage site) to the south and the Strait of Juan de Fuca to the north, opportunities for camping, hiking, biking, or visiting the famous lavender fields of Sequim are limitless. Contact Nancy Buckner, CEBS, SPHR, Human Resources, Olympic Medical Center 360 417 7231. Nbuckner@olympicmedical.org.

OLYMPIC MEDICAL CENTER

Saint Mary's HOSPITAL

Opportunity for a Pulmonary/Critical Care Physician at a teaching hospital!

Join our well-established team of Pulmonary, Critical Care & Sleep Physicians.

This is a hospital-employed position at a community teaching hospital with a Yale-affiliated Internal Medicine Residency Program. This exceptional opportunity is for a fellowship-trained Board Certified/Board Eligible Pulmonary/Critical Care Physician. Opportunity to practice some Sleep Medicine is available, if certified.

Position requires a strong interest in teaching and supervising Internal Medicine residents in the ICU and during an elective rotation in Pulmonary Medicine. The hospital is well equipped and has excellent Interventional Radiology and Anesthesia support. EBUS and Critical Care Ultrasound are available. Office is attached to the hospital in a medical office building and has a user friendly EMR. Weekend call will be 1:4.

This position offers growth opportunities, excellent salary with a bonus structure, a comprehensive benefit package, and a Yale clinical faculty appointment. The successful candidate must possess excellent communication and interpersonal skills, a strong clinical knowledge base, as well as outstanding patient care and teaching skills.

Since 1909, Saint Mary's Hospital has provided superior quality care to the people of the Greater Waterbury community.

At Saint Mary's Hospital, we truly value the expertise and dedication that our providers bring to our community. That's why we offer a supportive and cooperative Physician-Hospital relationship so you'll enjoy all of the tools and services you need for success in an environment that balances your career with your active lifestyle.

The Waterbury region provides the ideal environment for balancing successful careers with an active and enriching lifestyle.

Centrally located, with just a ninety-minute drive from NYC and two hours from Boston, the area has highly affordable housing, excellent school systems and a variety of recreation choices.

For additional information or to submit your CV please contact **Elena Geanuracos**: elena.geanuracos@stmh.org or 203.709.6223

WANTED

Pulmonary/Critical Care Physician. Pulmonary Consultants P.C. located in Phoenix Arizona is a Six-Doctor Pulmonary/Critical group seeking additional Physician due to practice growth. Diverse Hospital/office practice encompassing pulmonary, critical care medicine. Competitive salary/excellent benefits. Please send your CV via fax to 480 218-5706 or email to **aliciaga@PCofMesa.com** cell 480-466-2612

Disclaimer Chest Physician assumes the statements made in classified advertisements are accurate, but cannot investigate the statements and assumes no responsibility or liability concerning their content. The Publisher reserves the right to decline, withdraw, or edit advertisements. Every effort will be made to avoid mistakes, but responsibility cannot be accepted for clerical or printer errors.

CLASSIFIEDS

Also available at MedJobNetwork.com

PROFESSIONAL OPPORTUNITIES

KEEP UP-TO-DATE

Watch our Classified Notices for Postgraduate Course Information.

SLEEP STRATEGIES: The promise of Big Data Research to provide value to patients with sleep apnea

BY DR. EMILY KONTOS, SCM; AND
DR. SUSAN REDLINE, MPH, FCCP

A new Web-based community portal, www.MyApnea.Org, is mobilizing the largest community of patients and researchers ever created to work together to identify better ways to screen, treat, and prevent sleep apnea.

MyApnea.Org is the public face of the Sleep Apnea Patient-Centered Outcomes Network (SAPCON), one of 18 patient-powered research networks to improve comparative effectiveness research by focusing on patient-centered outcomes. This type of research asks: Of available treatment alternatives, which treatments are most effective and for which patients? The Patient-Centered Outcomes Research Institute (PCORI) (www.pcori.org) has established PCORnet, the National Patient-Centered Clinical Research Network which engages patients, care providers, and health systems in collaborative partnerships to develop platforms to efficiently conduct such fundamental research. Within PCORnet there are Patient-Powered Research Networks (PPRNs), focused on specific health conditions, such as sleep apnea (MyApnea.Org), that combine the complementary knowledge and insights of patients, caregivers, and researchers to help guide research that identifies effective and personalized treatments.


DR. KONTOS


DR. REDLINE

There has never been a more urgent time in sleep medicine for patient and stakeholder participation in such a national comparative effectiveness research initiative. With escalating health-care costs, payers are demanding higher levels of evidence to justify the use of diagnostic tests and treatments and are asking for data that provide value to the patient and health-care system. Many insurers restrict how sleep tests and treatments are delivered; however, those requirements often reflect a generalization of data from studies that were conducted at highly specialized referral centers and were not intended to be used without the support of a full team of committed sleep health professionals.

MyApnea.Org is inviting people with (or at risk of) sleep apnea to share information, provide support, and to help design, direct, and participate in sleep research. A broad and collaborative effort is what is needed to generate the evidence necessary for deciding which diagnostic studies and treatments are most effective. Studies of large numbers of individuals from across the United States (and the world) are needed to achieve the sample sizes necessary for identifying which patients benefit most (or might be harmed) from specific treatments. Rather than the traditional "one size fits all" approach to medicine and research, MyApnea.Org and PCORnet hopes to use information on health risk factors, biomarkers, background, and type of sleep apnea to tailor treatments that are likely to be most effective for individual patients. In such a way, a patient with a given set of risk factors (based on airway size, body fat distribution, time in REM sleep, etc) would be offered treatments most likely to benefit him or her. Furthermore, research that addresses the outcomes that matter to patients (eg, fatigue in women, behavioral problems in children) will ensure that the results are relevant and would improve the health and well-being of patients with sleep apnea. It is also an exciting time in sleep research as technological advances currently present numerous opportunities for improving sleep apnea diagnosis and management. Examples include telemedicine, newer ambulatory monitoring devices, mHealth devices, and sophisticated oral appliances and pressure devices. However, without good evidence on what works best, such technologies can be misused. MyApnea.Org is building a platform to conduct such large-scale patient-driven comparative effectiveness research.

Patient members of MyApnea.Org have the opportunity to complete a series of health-related surveys, nominate and vote on research questions, and can participate in forums to discuss how patient-centered research should be conducted. After completing the patient reported outcomes surveys, patients are able to see their answers in comparison with the rest of the patient community. In coming months, patients will have the opportunity to connect their wearable devices, and there are future plans to link patient-reported data with electronic medical records. Through these research communities, patients can identify what questions are most important and can co-develop proposals with health-care providers and scientists to address these needs.

Sleep researchers and clinicians are also encouraged to join MyApnea.Org. After becoming a member, providers are prompted to create their own specific landing page with a unique Web address and welcome message for their patients. These personalized Web links enable providers to promote the site among their patient panel, and when patients register for the site using the personalized link, providers and patients are connected within the MyApnea.Org database. Once a provider has at least 20 patients registered for the site, they are able to view the aggregate patient-reported outcomes for their patient panel and compare results against the entire patient community. These data could help many clinicians fulfill their maintenance of certification (MOC) requirements by monitoring patient-generated data to track adherence and other quality metrics. Additionally, sleep researchers have the ability to use the MyApnea.Org patient data in the development of grant proposals and other funding opportunities.

The success of MyApnea.Org lies in the breadth and diversity of its membership. The key message to pass along to patients is that it is now easier than ever for patients with sleep apnea to play an active role not only in their health care but in the research that is driving the decisions behind their health care. This is ever so important in the area of sleep health where the persisting gaps in knowledge are a significant determent to equitable health. MyApnea.Org already has enrolled more than 4,500 members in this national effort.

We encourage clinicians to refer patients with sleep apnea to join the patient-powered research network MyApnea.Org and to remind them that their data have the power to move the dial in sleep health. Similarly, we encourage clinicians and researchers to consider using the data provided within MyApnea.Org for future investigations.

Dr. Kontos is Instructor of Medicine at Harvard Medical School and an Associate Scientist at Brigham and Woman's Hospital; Dr. Redline is Peter C Farrell Professor of Sleep Medicine - Harvard Medical School, Brigham and Women's Hospital and Beth Israel Deaconess Medical Center, Boston.

EDITOR'S COMMENT

Precision medicine is a major initiative recently espoused by President Obama and members of the scientific and medical communities that offers the hope of improved categorization of disease, diagnostic modalities, and therapeutic options for each patient as an individual. As defined by the White House fact sheet, precision medicine is "an innovative approach to disease prevention and treatment that takes into account individual differences in people's genes, environments, and lifestyles" providing "clinicians tools to better understand the complex mechanisms underlying a patient's health, disease, or condition, and to better predict which treatments will be most effective." (www.whitehouse.gov) Obstructive sleep apnea is ripe for closer scrutiny in the spirit of precision medicine. Pathophysiologic mechanisms of sleep apnea, which include anatomic and nonanatomic features, vary among individual patients (Eckert et al. *Am J Respir Crit Care Med*. 2013;188[8]:996). Accordingly, treatment modalities vary in effectiveness among individuals, resulting in a push to investigate novel treatments such as hypoglossal nerve stimulation (Strollo et al. *N Engl J Med*. 2014;370[2]:139). Myapnea.org, as described by Drs. Kontos and Redline, is a potential game changer in its grassroots approach to the collection of big data to further the evaluation and management of sleep apnea. Patients and practitioners are encouraged to join the network and contribute to furthering precision medicine within the sleep community.

Dr. Jeremy A. Weingarten, FCCP

ZYFLO connect®

Savings. Shipping. Support.

ZYFLO CONNECT® PROGRAM – TERMS & CONDITIONS

HOW IT WORKS

If you are uninsured or have commercial insurance, including insurance purchased through the Affordable Care Act Exchange plans, Chiesi USA may help pay the out-of-pocket expenses (co-pay, co-insurance, deductibles) of your prescription. For patients taking ZYFLO CR® (zileuton) extended-release tablets, up to $2,500 per month will be provided, if you meet the eligibility requirements below. If the total costs of your out-of-pocket expenses are over $2,500 per month, you will be responsible for the outstanding balance.

ELIGIBILITY REQUIREMENTS

- You are either:
  - Uninsured, or
  - You are insured by commercial or private insurance and your insurance does not cover the full cost of ZYFLO CR
- Your prescriptions are not covered in full or in part by any state or federally funded insurance program, including but not limited to Medicare, Medicaid, Medigap, Veterans Affairs (VA) or Department of Defense (DOD) programs, or the Government Health Insurance Plan available in Puerto Rico (formerly known as "La Reforma de Salud"); patients who move from commercial to state or federally funded prescription insurance will no longer be eligible
- You are at least 18 years of age
- Void where prohibited by law

TERMS OF USE

- By accepting this offer and participating in the ZYFLO Connect program, you are representing and warranting to Chiesi that you currently meet the eligibility requirements described above and will comply with these Terms of Use.
- Out-of-pocket benefit equals an amount up to $2,500 per month (maximum benefit of $30,000 per year) for ZYFLO CR. Patient is responsible for applicable taxes, if any.

  EXAMPLE: If your monthly ZYFLO CR prescription co-pay or out-of-pocket cost is $3,000, eligible patients will only pay $500 per month for ZYFLO CR, a savings of $2,500 off of their co-pay or total out-of-pocket costs. If your co-pay or out-of-pocket costs are no more than $2,500, you pay $0. For a mail-order 3-month prescription, your total maximum savings will be $7,500 ($2,500 x 3).
- If a patient exceeds the maximum monthly benefit of $2,500, the patient will be responsible for the outstanding balance.
- Patients, pharmacists, and prescribers cannot seek reimbursement from health insurance or any third party, for any part of the benefit received by the patient through this offer.
- Your acceptance of this offer confirms that this offer is consistent with your insurance and that you will report the value received as may be required by your insurance provider.
- Only valid in the United States or Puerto Rico; this offer is void where restricted or prohibited by law.
- No membership fees.
- The ZYFLO Connect program is not insurance.
- The ZYFLO Connect program cannot be combined with any other rebate/coupon, free trial, or similar offer for the specified prescription.
- The ZYFLO Connect program expires on December 31, 2016.
- The ZYFLO Connect program is limited to one per person.
- Chiesi USA reserves the right to rescind, revoke, or amend this offer at any time without notice.
- **The ZYFLO Connect program is only offered through distribution from Foundation Care, a full-service pharmacy serving patients in all 50 states and Puerto Rico.**

  Foundation Care, 4010 Wedgeway Court, Earth City, MO 63045 Phone: (844) 699-9356

Chiesi

ZYFLO CR®
(zileuton) extended-release tablets

ZYFLO connect®

Savings. Shipping. Support.

$0 monthly co-pay*
up to $2,500 per month in savings on every prescription

FREE next-day delivery
direct to your patient's door

Reimbursement support
by phone to help with the PA process if required

Pharmacist on call 24/7
to answer questions

Refill reminder phone calls
from a ZYFLO Connect pharmacist

Simple and streamlined
enrollment process via phone, fax, or EMR

CONNECT patients with VALUABLE BENEFITS

Contact your patients about these benefits today

Visit myZYFLO.com or **Call 1-844-ZYFLO-RX**

*Terms and conditions apply. Please see full Terms and Conditions on adjacent page.

Chiesi