Halting smoking boosts LDCT benefits

BY KATIE WAGNER LENNON
Frontline Medical News

Smoking abstinence for 7 years results in a 20% reduction in death from lung cancer—a benefit that is comparable to three rounds of annual screening with low-dose helical computed tomography (LDCT)—in asymptomatic individuals with at least a 30-pack-year smoking history, based on a secondary analysis of 50,263 participants in the National Lung Screening Trial (NLST).

Not smoking for 7 years

See Abstinence · page 6

Blood test predicts TB progression

BY MARY ANN MOON
Frontline Medical News

A international team of researchers has developed a blood test that identifies the 5%-10% of patients infected with latent tuberculosis who are likely to progress to active TB, up to 18 months before they show any sign of illness, according to a report published in the Lancet.

Worldwide, one-third of the apparently healthy population is infected with Mycobacterium tuberculosis, but only a fraction will develop active TB during their lifetimes. Until now, there has been no way to predict which of these people will progress and become ill.

Treating all latently infected people in endemic areas for the necessary 6-9 months isn’t feasible, but a test that distinguishes which cases will become active would allow targeted preventive therapy. This could potentially interrupt the global spread of TB, said Daniel E. Zak, Ph.D. of the Center...
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.
Start preserving more lung function for patients with IPF$^4$

- Esbriet had a significant impact on lung function vs placebo in ASCEND$^3,4$†
  - 48% relative reduction in risk of a meaningful decline in lung function at 52 weeks for patients on Esbriet vs placebo (17% vs 32%; 15% absolute difference; $P<0.001$)
  - 2.3× as many patients on Esbriet maintained their baseline function at 52 weeks vs placebo (23% vs 10% of patients; 13% absolute difference; $P<0.001$)

- Esbriet delayed progression of IPF vs placebo through a sustained impact on lung function decline in ASCEND$^3,4$†
  - Patients on Esbriet maintained an average of 193 mL more lung function at 52 weeks vs placebo (–235 mL vs –428 mL; $P<0.001$)

- No statistically significant difference vs placebo in change in %FVC or decline in FVC volume from baseline to 72 weeks was observed in CAPACITY 006$^3,5$

- Esbriet has been approved outside the US since 2011, with approximately 15,000 patients treated with pirfenidone worldwide$^2$

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

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 (CLcr $\geq 50-80$ mL/min), moderate (CLcr $30-50$ mL/min), or severe (CLcr 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.

Post hoc analyses of benefits

Reslizumab from page 1

two trials included close to 1,000 patients aged 12-75 years with baseline blood eosinophil counts of at least 400 cells/μl, and inadequate controlled asthma despite being on at least moderate-dose inhaled corticosteroids. The primary endpoint – frequency of clinical asthma exacerbations – was reduced by 54% with reslizumab compared to placebo (Lancet Respir Med. 2015 May;3(5):355-66).

For the first post hoc analysis, Dr. Steven F. Weinstein compared 52-week outcomes in 250 patients with chronic sinusitis, including 150 who also had nasal polyps, in juxtaposition to the total two-study population of 933 eosinophilic asthma patients. Of note, aspirin sensitivity was present in 37% of those with chronic sinusitis and nasal polyps (CSwNP) compared to 11% of total participants. The CSwNP group had higher blood eosinophil levels, too: an average of 884 cells/μl, compared with 635/μl in the study population as a whole.

The frequency of clinical asthma exacerbations – was reduced by

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>% of Patients (0 to 118 Weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>36% 16%</td>
</tr>
<tr>
<td>Rash</td>
<td>30% 10%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>24% 15%</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>27% 25%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>26% 20%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>26% 19%</td>
</tr>
<tr>
<td>Headache</td>
<td>22% 19%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>19% 7%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>18% 11%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13% 6%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>13% 5%</td>
</tr>
<tr>
<td>Gastro-esophageal Reflux Disease</td>
<td>11% 7%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>11% 10%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>10% 7%</td>
</tr>
<tr>
<td>Weight Decreased</td>
<td>10% 5%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>10% 7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>ESBRIET® (pirfenidone)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Reaction</td>
<td>% of Patients (0 to 118 Weeks)</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>27% 25%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>26% 20%</td>
</tr>
<tr>
<td>Headache</td>
<td>22% 19%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>19% 7%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>18% 11%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13% 6%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>13% 5%</td>
</tr>
<tr>
<td>Gastro-esophageal Reflux Disease</td>
<td>11% 7%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>11% 10%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>10% 7%</td>
</tr>
<tr>
<td>Weight Decreased</td>
<td>10% 5%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>10% 7%</td>
</tr>
</tbody>
</table>

Adverse reactions occurring in ≥5 to <10% of ESBRIET-treated patients were respiratory infections (28% vs. 18%), dyspepsia (26% vs. 19%), and abdominal pain (13% vs. 8%). Adverse reactions occurring in ≥3% of ESBRIET-treated patients were headache (18% vs. 12%), upper respiratory tract infection (11% vs. 7%), and abdominal pain (10% vs. 4%).
ESBRIET® (pirfenidone)

7 DRUG INTERACTIONS
7.1 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 CYP1A2 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 CYP1A2 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 is used at a dosage of 750 mg twice daily, it 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.

7.2 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, discontinuation of 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]

8 USE IN SPECIFIC POPULATIONS
8.1 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 (oral dosage approximately 3 times the MRDD in adults, on a mg/m^2 basis) revealed no evidence of impaired fertility or harm to the fetus due to pirfenidone. The results of the presence of maternal toxicity, acyclic/irregular cycles (e.g., prolonged estrous cycles) 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 newborns, 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). The peak period of organogenesis in rats occurs from 6 to 18 days of gestation. 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.

8.3 Nursing Mothers
Evidence and effectiveness of ESBRIET in pediatric patients have not been established.

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

8.5 Geriatric Use
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.

Among all subjects with chronic sinusitis who received reslizumab, the reduction in exacerbations was intermediate at 70%, with 2.81 episodes in controls and 0.83 episodes with reslizumab.

Clinical asthma exacerbations were defined as the use of systemic steroids by patients not already on such medication or at least a twofold increase in doses of inhaled or systemic corticosteroids for at least 3 days.

The placebo-subtracted improvement in lung function from baseline to 52 weeks in reslizumab-treated patients was 326 mL in the CSwNP group, 235 mL in all patients with chronic sinusitis, and 109 mL in the overall study population, according to Dr. Weinstein, an allergist-immunologist practicing in Huntington Beach, Calif.

A 0.5-point improvement on the validated Asthma Quality of Life Questionnaire (AQOL) is accepted by researchers as the minimum for demonstrating clinically significant benefit. The 52-week placebo-subtracted improvement on this measure was 0.69 points in the reslizumab-treated CSwNP group, 0.47 in the total cohort of asthmatics with chronic sinusitis, and 0.27 points in the overall reslizumab-treated population.

Similarly, the average placebo-subtracted improvement on the Asthma Control Questionnaire–6 was 1.45 points in reslizumab-treated patients with CSwNP, a sixfold greater response than seen in the total study population, Dr. Weinstein noted.

A similar pattern of greater-than-average efficacy with reslizumab on both primary and secondary study endpoints was seen in the 77 patients aged 65 years and older as compared with those aged 18-64 years, according to Dr. David Bernstein, professor of medicine and environmental health at the University of Cincinnati.

Older patients made up only a small fraction of total subjects in the two trials, yet asthma affects an estimated 7% of Americans age 65 and up, and rates of asthma hospitalization and mortality are higher than in younger patients, he noted.

With reslizumab, the older cohort had a 67% reduction in the frequency of asthma exacerbations, while the younger patients had a 53% reduction.

Measures on the AQOL, the Asthma Control Questionnaire–7, and the Asthma Symptom Utility Index were consistently better in older as compared to younger reslizumab-treated patients. Only the older group had minimal clinically significant improvement in all three measures.

The two post hoc analyses were funded by Teva Pharmaceuticals. Both investigators serve on advisory boards for Teva and multiple other pharmaceutical companies.
Smoking, LDCT

Abstinence from page 1

plus screening for lung cancer with LDCT conferred an additional 10% reduction in lung cancer mortality. Similar patterns for smoking cessation benefits were noted for overall reduction in lung cancer mortality. LDCT conferred an additional 10% from smoking and had been screened with a chest x-ray, the risk of dying of lung cancer decreased by 3%.

In contrast, lung cancer mortality increased by 10% for each 10-pack-years smoked for those screened with LDCT (HR, 1.10; 95% CI, 1.08-1.13). In both screening groups, “an additional 6% risk of death from all causes (was seen) for each additional 10 pack-years smoked.” In addition, black study participants who had quit smoking at trial entry had “a more pronounced benefit” from having done so, compared with the white study participants (HR, 0.53, 95% CI, 0.28-1.0).

Dr. Tannen, one of this secondary analysis’s authors reported receiving grants from ACCP OneBreath Foundation and from Olympus America, Cook, and the American Cancer Society for other work.

kiennon@frontlinemedcom.com

Smoking cessation paramount

T

his secondary analysis was limited by the fact that the National Lung Screening Trial does not have information about smoking cessation or persistence during the trial. The finding of black former smokers having a hazard rate for lung cancer mortality of 0.53, compared with white former smokers, was reassuring because there is evidence that African Americans are at higher risk for lung cancer at lower smoking intensities than whites.

While this secondary analysis suggests that screening for lung cancer can reduce lung cancer death risk, lung cancer screening alone is not adequate for preventing the disease. Screening must be linked to smoking cessation efforts in those who are current smokers and may need to follow criteria that are different from those used in the NLST. Implementation of lung cancer screening will be a serious challenge that must be linked to smoking cessation efforts in those who are current smokers at the time they enter a screening program, both for Centers for Medicare & Medicaid Services reimbursement and for medical appropriateness.

Dr. Christine D. Berg is with Johns Hopkins Medicine, Baltimore, and the division of cancer epidemiology and prevention at the National Cancer Institute, Bethesda, Md. She made these remarks in an editorial accompanying Dr. Tanner’s report (J Respir Crit Care. 2016 March 1. doi: 10.1164/rcrm.201511-2270ED). She reported receiving personal fees from Medial CS, and she was the study director of the NLST.
Cold turkey better for smoking cessation

BY MARY ANN MOON
Frontline Medical News

Quitting smoking abruptly leads to higher abstinence rates both at 4 weeks and 6 months, according to a report published online in the Annals of Internal Medicine.

Worldwide guidelines for smoking cessation generally recommend abrupt cessation over a gradual reduction in smoking, based on data from observational studies. However, a recent review of 10 randomized trials concluded that quitting “cold turkey” produces only slightly higher quit rates, said Nicola Lindson-Hawley, Ph.D., of the department of primary care health services, University of Oxford (England), and her associates.

They compared the two approaches in a noninferiority trial involving 697 adults treated at 31 primary care practices in England during a 2.5-year period. The study participants smoked at least 15 cigarettes per day and had an end-expiratory carbon monoxide concentration of at least 15 parts per million.

The average age was 49 years, and the study population was evenly divided between men and women. Their mean score on the Fagerström Test for Cigarette Dependence was 6, indicating a high degree of dependence.

These participants were randomly assigned either to stop smoking abruptly on a quit date 2 weeks from baseline (355 patients) or to stop gradually, by reducing their smoking, with the eventual goal of reducing their smoking by half at 1 week, by half again during the second week, and completely from baseline, by half again during the second week, and completely by a quit date 2 weeks from baseline. The latter group was given a choice of three structured reduction programs to follow before the quit date, as well as nicotine patches and a choice of short-acting nicotine replacement products (gum, lozenges, nasal sprays, sublingual tablets, inhalators, or mouth sprays). The abrupt-cessation group received only the nicotine patches just before the quit day. Both groups received identical behavioral counseling, nicotine patches, and nicotine replacement products after the quit date.

The primary outcome measure, abstinence at 4 weeks, was achieved by 49% of the abrupt-cessation group, compared with only 39.2% of the gradual-cessation group (relative risk, 0.80). Thus, gradual cessation did not prove to be non-inferior to abrupt cessation. The secondary outcome measure of abstinence at 6 months also was superior for the abrupt-cessation group (22%) over the gradual-cessation group (15.5%). Dr. Lindson-Hawley and her associates reported (Ann Intern Med. 2016 Mar 15. doi: 10.7326/M14-2805).

Most of the between-group difference was attributed to the fact that fewer participants in the gradual-cessation group actually attempted to quit on their quit date (61.4% vs. 71.0%). Relapse rates were similar between the two study groups at 4 weeks (36.2% vs. 31.0%) and at 6 months (74.8% vs. 69.1%).

“These results imply that, in clinical practice, we should encourage persons to stop smoking abruptly and not gradually,” Dr. Lindson-Hawley and her associates wrote. “However, gradual cessation generally recommend abrupting abruptly increases long-term cessation rates in smokers who want to quit. However, a gradual approach to smoking cessation still may be useful for some smokers, so that method shouldn’t be entirely abandoned just yet.

Many smokers try several times to quit abruptly but are not successful. They may not wish to set another abrupt quit date for fear of ‘failing’ yet again. However, they may instead respond well to gradually reducing their smoking, with the eventual goal of reducing it all the way to zero.

These findings raise important questions about how clinicians should approach patients who smoke and are ready to quit.

Dr. Gabriela S. Ferreira and Dr. Michael B. Steinberg are at the Robert Wood Johnson Medical School in New Brunswick. Dr. Ferreira reported having no relevant financial disclosures; Dr. Steinberg reported receiving personal fees from Arena Pharmaceuticals, Major League Baseball, and Pfizer outside of this work. Their remarks (Ann Intern Med. 2016 Mar 15. doi: 10.7326/M16-0362) appeared in an editorial that accompanied Dr. Lindson-Hawley’s report.

Excess annual drug costs for COPD + asthma vs. COPD alone

Excess annual cost

Note: Based on data for 22,565 subjects in each of the two groups (COPD, COPD + asthma).


COPD with asthma more costly than COPD alone

BY RICHARD FRANKI
Frontline Medical News

Health care costs almost $400 more per year for patients with chronic obstructive pulmonary disease who have a history of asthma, based on records of over 45,000 adults in British Columbia, reported Dr. Mohsen Sadatsafavi of the University of British Columbia, Vancouver, and his associates (Ann Am Thorac Soc. 2016 Feb;13(2):188-96).

The largest component of that excess was medication costs. These excesses were somewhat offset by hospitalization costs, which were $196 less per year for the COPD + asthma group, the investigators said.

Inhaled corticosteroids/long-acting beta-agonists cost almost $178 more per year for the COPD + asthma patients. Inhaled corticosteroids were next, with a cost excess of $64 annually, followed by long-acting muscarinic agents ($59), short-acting beta-agonists ($46) and leukotriene receptor agonists ($19).

Don’t abandon gradual quitting yet

The trial by Nicola Lindson-Hawley, Ph.D., is well designed and suggests that setting a quit date and quitting abruptly increases long-term cessation rates in smokers who want to quit. However, a gradual approach to smoking cessation still may be useful for some smokers, so that method shouldn’t be entirely abandoned just yet.

Many smokers try several times to quit abruptly but are not successful. They may not wish to set another abrupt quit date for fear of “failing” yet again. However, they may instead respond well to gradually reducing their smoking, with the eventual goal of reducing it all the way to zero.

These findings raise important questions about how clinicians should approach patients who smoke and are ready to quit.

Dr. Gabriela S. Ferreira and Dr. Michael B. Steinberg are at the Robert Wood Johnson Medical School in New Brunswick. Dr. Ferreira reported having no relevant financial disclosures; Dr. Steinberg reported receiving personal fees from Arena Pharmaceuticals, Major League Baseball, and Pfizer outside of this work. Their remarks (Ann Intern Med. 2016 Mar 15. doi: 10.7326/M16-0362) appeared in an editorial that accompanied Dr. Lindson-Hawley’s report.
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 particle with multiple drug crystals

1
Visit Co-SuspensionParticles.com to Learn More

CO-SUSPENSION TECHNOLOGY

All images are for illustrative purposes only.

Possibly useful for monitoring treatment

Blood test from page 1

for Infectious Disease Research, Seattle, and his associates.
Such a test also might be used to assess treatment response, as well as to enroll only the highest-risk carriers of M. tuberculosis in trials of new drugs and vaccines, they added.
The investigators began by analyzing gene expression in peripheral whole-blood samples from 6,363 apparently healthy adolescents participating in a South African cohort study who were followed for 2-4 years for the development of active TB. They compared RNA-sequencing data from 46 participants who developed active TB against that from 107 matched control subjects who remained healthy and identified a candidate 16-gene risk signature for TB progression.

“Robust discrimination between progressors and controls based on the expression of the gene pairs in the signature was readily apparent,” the researchers said.
In this subgroup of patients, the risk signature had a 71.2% sensitivity for predicting active TB during the 6 months preceding diagnosis, a 62.9% sensitivity during the 12 months preceding diagnosis, and a 47.7% sensitivity during the 18 months preceding diagnosis.

The specificity was 80.6%.
To validate their findings, the investigators adapted the risk signature to a more practical PCR platform and used it to predict the risk of active TB in the remainder of the study population. The risk signature remained comparably sensitive and specific in this analysis.

To validate their findings in an independent cohort, Dr. Zak and his associates analyzed whole-blood samples from 4,466 apparently healthy adults from South Africa and the Gambia who were participating in a study of household contacts of patients with newly diagnosed active TB.

Continued on following page

Potential to transform TB control worldwide

The current TB epidemic is sustained by the emergence of new cases from the 2 billion people worldwide who have latent TB infection, and from the subsequent infection of their contacts. A test that identifies which people with latent infection will progress to active infection would transform TB control by allowing target-ed treatment that would prevent these new cases from emerging.
Another significant finding from the work of Dr. Zak and his associates is that differences in gene expression were detected months before TB symptoms developed. This suggests that progressors have an immune response well before they are diagnosed, that their immune response differs from that of people who remain well, and that the progression from latent to active TB infection is a continuum in the battle between host and pathogen.

Dr. Michael Levin and Dr. Myrissni Kafourou are in the section for pediatric infectious diseases at Imperial College London. They reported being members of an EU-funded TB vaccine consortium and previously worked on an EU-funded study of TB biomarkers, both of which included some of Dr. Zak’s associates. Dr. Levin and Dr. Kafourou made these remarks in an editorial comment accompanying Dr. Zak’s report (Lancet. 2016 Mar 23. doi: 10.1016/S50140-6736(16)00165-3).

Trial finds fluticasone-salmeterol inhalers to be safe

BY M. ALEXANDER OTTO

Frontline Medical News

LOS ANGELES – Fluticasone-salmeterol inhalers (Advair) are as safe and more effective than fluticasone monotherapy inhalers are for patients with moderate to severe asthma, according to a randomized trial from its drug maker, GlaxoSmithKline, presented at the annual meeting of the American Academy of Allergy, Asthma and Immunology and simultaneously published online in the New England Journal of Medicine.
The study is the first of several that the Food and Drug Administration required from Glaxo and other manufacturers in 2010 to evaluate the safety of long-acting beta-2 agonists (LABAs) such as salmeterol when used in combination with inhaled corticosteroids, after it became clear that LABAs, when used alone, increase the risk of serious asthma complications, including death (N Engl J Med. 2016 Mar 6; doi: 10.1056/NEJMoa1511049).
Current black box warnings on fluticasone-salmeterol (Advair), Merck’s mometasone-formoterol inhaler (Dulera), and AstraZeneca’s budesonide-formoterol combo (Symbicort) note that data are “inadequate to determine” if concomitant steroids mitigate the risk of LABAs.

Merck and AstraZeneca’s studies are ongoing.

“This is the first really large study to show a decrease in exacerbations with [fluticasone-salmeterol],” principal investigator Dr. David Stempel, with Glaxo’s Respiratory Clinical Development program in Durham, N.C., said at the meeting.
However, because “patients with a history of life-threatening or unstable asthma” – including those who, at any point, had been intubated for asthma – “were excluded from the study, our results cannot be extrapolated to such patients,” the researchers wrote.
Adults and adolescents at least 12 years old, with a history of severe asthma exacerbations requiring the use of inhaled glucocorticoids or hospitalization in the previous year, but not in the month before enrollment, were included.
There were 5,834 subjects randomized to fluticasone-salmeterol and 5,845 to fluticasone alone, both for 26 weeks.
Adherence to the study medications was 95%.
There were 36 serious asthma-related events – endotracheal intuba-tion or hospitalization – in 34 patients (0.58%) in the fluticasone-salmeterol group, and 38 events in 33 patients (0.56%) in the fluticasone-only group.

While 480 fluticasone-salmeterol patients (8%) had at least one severe asthma exacerbation, at least one severe exacerbation occurred in 597 fluticasone-only patients (10%).

The specificity was 80.6%.
To validate their findings, the investigators adapted the risk signature to a more practical PCR platform and used it to predict the risk of active TB in the remainder of the study population. The risk signature remained comparably sensitive and specific in this analysis.

To validate their findings in an independent cohort, Dr. Zak and his associates analyzed whole-blood samples from 4,466 apparently healthy adults from South Africa and the Gambia who were participating in a study of household contacts of patients with newly diagnosed active TB.

Continued on following page

Highest risk patients excluded

At first glance, these results appear to be reassuring. However, patients were excluded from the trial if they had a history of life-threatening or unstable asthma. Thus, it is not surprising that only two patients in the trial had life-threatening asthma and that adherence to study medication was 95%, a rate unheard of in clinical practice.
What practical conclusions can be drawn from this study? It is clear that among patients with asthma who have not had life-threatening episodes in the past and are highly adherent to their drug regimen, it is likely that salmeterol together with fluticasone in a single inhaler is safe. For these patients and this combination, the black-box warning should be lifted. This is an important result, and it stresses that most patients with asthma, and especially those without serious episodes, can reach high levels of symptom control and avoid frequent exacerbations by simply using their inhalers every day.
What remains unanswered is whether this conclusion applies to patients who have the most severe and unstable disease, since these are the patients for whom guidelines still recommend the use of LABAs [long-acting beta-2 agonists], combined with inhaled glucocorticoids, as first-line treatment. For these patients, the safe clinical approach is to maintain the same precautions in using fluticasone-salmeterol that have been recommended until now for all patients with asthma.

Dr. Fernando Martinez is a professor of pediatrics and director of the Asthma/Airway Disease Research Center at the University of Arizona, Tucson. He made his comments in an editorial (N Engl J Med. 2016 Mar 16. doi: 10.1056/NEJMec1601040).
Continued from previous page

During follow-up, 43 progressors and 172 control subjects were identified at the South African study site, and 30 progressors and 129 control subjects were identified at the Gambian study site.

The risk signature again reliably distinguished patients who progressed from latent to active TB from those who didn’t progress, months before any sign of illness surfaced.

When applied to combined data from 4 studies of HIV-uninfected South African adults involving 130 prevalent TB cases and 230 controls, the signature discriminated between patients with active TB and controls with 87% sensitivity and 97% specificity, ” the investigators noted.

Adapting the risk signature further to microarrays so that it could be used in other datasets, the researchers found that it readily distinguished latent from active TB infection in stored samples from more cohorts from the United Kingdom, South Africa, and Malawi. In these cases the risk signature also distinguished active TB from other pulmonary diseases and from other diseases of childhood, and did so regardless of whether the study subjects were coinfected with HIV or not.

“Finally, applying the signature to data from a treatment study showed that the active TB signature gradually disappears during 6 months of therapy,” Dr. Zak and his associates wrote (Lancet 2016 March 23. doi:10.1016/S0140-6736(15)01316-1).

These latter observations suggest that the risk signature may reflect the TB bacterial load in the lung.

The study results were particularly encouraging given the marked diversity among these study populations.

The participants had different age ranges, different infection or exposure status, distinct ethnic and genetic backgrounds, different local epidemiology, and different circulating strains of M. tuberculosis. “Our results … pave the way for the establishment of diagnostic methods that are scalable and inexpensive.

An important first step would be to test whether the signature can predict TB in the general population, rather than the select populations included in this project,” the investigators added.

This study was funded by the Bill and Melinda Gates Foundation, the National Institutes of Health, the European Union, the South African Medical Research Council, and Aeras. The researchers reported having no relevant financial disclosures.
PULMONARY PERSPECTIVES®: Three lung function tests in preschoolers

**BY DR. PELTON A. PHINIZY AND DR. STEPHANIE LOVINSKY-DESR**

Pediatricians are often taught that children are not simply small adults. Unique aspects of normal lung development and respiratory pathology in small children require clinicians and researchers to appreciate the applicability and utility of pulmonary function testing modalities that were originally designed for adults. Evaluation of lung function in preschool children (ages 3 to 7 years) can be especially important for clinical assessment, tracking disease progression, and judging utility/effectiveness of medication for many respiratory disorders (e.g., wheeze, chronic lung disease of prematurity, and cystic fibrosis). However, testing in this particular age group has certain technical challenges specific to the maneuver required for each test. In addition, young children can have short attention spans and, thus, need to be supported and engaged throughout the testing maneuver. Here, we review three methods of assessing pulmonary function: spirometry, impulse oscillometry (IOS), and fractional exhaled nitric oxide (FeNO); with emphasis on the advantages, disadvantages, and applicability in preschool children.

**Spirometry**

Spirometry is the most widely used method of measuring pulmonary function, and reliable results can be obtained in many preschool children. The maneuver requires active participation as the child inhales to total lung capacity and exhales rapidly and forcefully to residual volume. The forced vital capacity and forced expiratory volume in the first second (FEV₁), among other values generated from the study, are then compared either to reference values or to previous results from the same child. However, preschool children are frequently unable to exhale forcefully for greater than a few seconds (6 seconds is recommended). Thus, the FEV₁ in 0.5 seconds (FEV₁₅₀) or 0.75 seconds (FEV₁₇₅) is often used instead of the FEV₁, as an indicator of airflow limitation. In order to overcome potential difficulties with performing acceptable and reproducible maneuvers, incentives are built into the software to encourage maximal effort. Performing spirometry pre- and post-bronchodilator treatment can be helpful in identifying a reversible component to lower airway obstruction in the wheezy preschool child. In addition, these studies can be particularly helpful in the premature child to help distinguish fixed vs. reversible lower airway obstruction. However, it has been suggested that spirometry may not be sensitive enough in some milder cases of wheezing to detect obstruction (Marotta et al. *J Allergy Clin Immunol.* 2003;112(2):317). Spirometry is also very useful in children with cystic fibrosis. Reductions in air flow can support the decision for treatment with antibiotics in a child who might not be able to clearly articulate symptoms of an acute exacerbation.

Several portable spirometry devices are now readily available for use in both the clinical and research settings. Furthermore, normative reference values exist within this age group allowing for longitudinal assessments of lung function and growth in comparison to healthy populations; albeit, reference values are not well validated for some subpopulations of races/ethnicities.

**Impulse Oscillometry (IOS)**

IOS is a noninvasive method for measuring the impedance of flow in the respiratory system. Sound waves are generated by a loudspeaker and flow via a mouthpiece through the airways while the child is spontaneously tidal breathing. The respiratory system resistance (frictional losses) and reactance (elasticity) are then calculated from the resulting signal. IOS is often referred to as “effort-independent” and is generally perceived to be easier for preschool children because there is minimal active participation required. However, in order to obtain acceptable results, the child should perform a minimum of three trials, to 45 seconds each, in a relaxed state. One recent study in a longitudinal birth cohort of over 400 children reported fewer acceptable trials with IOS compared with spirometry in 3- to 5-year-olds (Kattan et al. *Am Thoracic Soc Conf Abstr*; 2013:A3695). Unacceptable trials may result from swallowing, vocalizing, breath holding, or air leaks. While spirometry is a classic test used to determine change in airway obstruction in response to bronchodilators, IOS may be more sensitive in detecting small changes in airway resistance or lung compliance. In fact, IOS is thought to be more sensitive to signs of improvement in asthma following initiation of controller medications that may not be ascertainable by spirometry (Guilbert et al. *N Engl J Med.* 2006;354(19):1895). Also, during methacholine challenge testing, IOS can detect mild airway obstructions in children at lower doses and earlier than changes in FEV₁ (Schulze et al. *Respir Med.* 2012;106(5):627). Thus, in addition to its clinical applicability, IOS might be a more sensitive tool in research settings, for example, in identifying acute or chronic airway changes in response to environmental exposures.

The device for measuring IOS can be relatively compact and lightweight consisting of a box for the hardware and an arm support for the mouth piece; however, it does require connection to a computer. Additionally, reference values for IOS are limited, and normative values need to be established to account for potential differences by sex, age, and height.

**Fractional Exhaled Nitric Oxide**

FeNO is another tool for assessment of respiratory disease in young children, particularly in the evaluation of allergic airway disease, such as asthma. This noninvasive test measures the amount of endogenously produced nitric oxide in the airway, the majority of which is produced by epithelial and inflammatory cells in chronic airway inflammation. For adults, quality standards require inhalation to total lung capacity and then exhalation against a backpressure of 5 cm H₂O at a rate of 50 mL/s for 10 seconds. Recent work suggests that young children may not need to exhale for a full 10 seconds to reach a steady state level of exhaled NO adequate for measurement because of their smaller lung volumes. Shorter times of 6 seconds have been suggested and are being validated (Heijenskold-Rentzhog et al. *Pediatr Allergy Immunol.* 2015;26(7):662).

FeNO may be a more sensitive test for identifying airway inflammation associated with mild asthma compared with spirometry. A recent study in 5- to 6-year-old children demonstrated that FeNO was significantly associated with both the presence of wheeze and airway hyperreactivity, whereas spirometry and IOS were not (Lee et al. *J Asthma.* 2015;52(10):1054). However, there are limited data to support the utility of FeNO in assessing response to treatment. A Cochrane review reported no clear benefit when FeNO was compared with the use of clinical symptoms and spirometry to help guide chronic treatment.

Continued on following page
Isavuconazole equivalent to voriconazole for aspergillusosis

BY CHRISTINE KILGORE

The broad-spectrum triazole isavuconazole was as effective as voriconazole in patients with suspected invasive mold disease and caused significantly fewer drug-related adverse events, particularly those of the skin, eyes, and hepatobiliary system, a randomized double-blind study of 516 adults has shown.

The newer agent “could allow safer therapy” for the primary treatment of invasive aspergillusosis and other mold disease than standard therapy with voriconazole, researchers for the industry-sponsored SECURE trial say in a report in the Lancet.

The researchers assessed the safety and efficacy of isavuconazole versus voriconazole in patients with invasive mold infection. Patients were recruited

Continued from previous page

ic therapy in children with asthma (Petsky et al. Cochrane Database Syst Rev. 2009;4:CD006340). Yet, FeNO is increasingly used to detect patients who have current wheeze and predict future asthma (Singer et al. Allergy. 2013;68[4]:531). Thus, FeNO might be the better choice for detecting small amounts of increased airway inflammation in preschool children who may eventually develop asthma.

There are two types of analyzers for FeNO. The first, a chemiluminescence analyzer, provides high quality data but is more expensive, difficult to transport, and more often used in research settings. The second, an electrochemical sensor device, is less expensive and more easily portable but has limited sensitivity compared with the chemiluminescence analyzers. Similar to spirometry, visual incentive programs have been developed to assist with subject cooperation. Nonetheless, even with shorter exhalation cutoff times and incentive programs, young children may have difficulty with the maneuver.

While we have reviewed three of the most commonly used and feasible pulmonary function testing methods used today in preschool children, there are several other modalities available for this young population. Other tests include the interrupter technique, tidal breathing analysis, and the lung clearance index. These tests also have advantages and disadvantages. Ultimately, there is no “best test” for all situations, and a test is only as good as the question being asked. It must also be emphasized that proper training of the person conducting the study is critical for all methods of measuring pulmonary function. Despite potential challenges in this young age group, pulmonary function testing can be both practical and useful in the diagnosis and management of respiratory conditions in preschool children.

Dr. Phinizy and Dr. Lovinsky-Desir are from the Division of Pediatric Pulmonology, Department of Pediatrics, Columbia University Medical Center, New York, NY.
ed from 102 centers across 26 countries over a 7-year period and were randomized to receive either drug. In the study group of 516 adults with suspected invasive mold infection who received at least one dose of either drug, isavuconazole was noninferior to voriconazole, based on all-cause mortality at 6 weeks. All-cause mortality at 6 weeks in this intention-to-treat group, of whom more than 80% had hematologic malignant disease, was 19% in the isavuconazole group and 20% in the voriconazole group. All-cause mortality “provides the most objective and reproducible effect of therapy, and approximates best the attributable mortality, because deaths due to competing causes occur increasingly after 6 weeks,” Dr. Johan A. Maertens of the UZ Leuven (Belgium), and his associates wrote. Secondary endpoints included overall response among patients found by an independent review committee to have proven or probable invasive mold disease – the study’s modified intention-to-treat population – as well as all-cause mortality at days 42 and 84.

All-cause mortality in this modified intention-to-treat group, as well as in patients found to have...
proven or probable invasive aspergillosis, specifically, supported the study’s primary findings (Lancet 2016 Feb;387:760-9).

Nearly all patients in the study had at least one adverse event, and the proportion with serious adverse events was similar between the treatment groups. However, patients treated with isavuconazole had a significantly lower frequency of hepatobiliary disorders, eye disorders, and skin or subcutaneous disorders.

And overall, significantly fewer patients reported drug-related adverse events with isavuconazole (42% of patients) than with voriconazole (60% of patients). Discontinuation from adverse events, moreover, was significantly less common among isavuconazole-treated patients.

Of the 516 patients in the intention-to-treat group, 53% were confirmed to have proven or probable invasive mold disease, and more than 80% of the mycologically documented cases were Aspergillus infections. Enrollment of patients with possible invasive mold disease at the start “reflects the real-life strategy of early initiation of antifungal treatment,” the investigators say.

Isavuconazonium sulfate was

Continued on following page
Continued from previous page

approved in 2015 by the FDA for the treatment of invasive aspergillosis and invasive mucormycosis. Voriconazole is the current standard for the primary treatment of invasive aspergillosis and is recommended for some other mold infections, but it is not active against mucormycosis and has “highly variable nonlinear pharmacokinetics in adults,” which has triggered recommendations for drug monitoring.

Therapeutic monitoring aimed at individualizing dosage regimens to improve response and prevent adverse events became the standard of care in some institutions during the study period (2007-2013). The study used the labeled dose of voriconazole, however, and did not address the efficacy of either drug with drug monitoring.

The study also excluded patients with AIDS, abnormal liver or renal function, and those receiving antifungal prophylaxis with a mold-active triazole – factors that may limit generalizability of the findings.

Funding for the study was provided by Astellas Pharma Global Development and Basilea Pharmaceutica International. Dr. Maertens disclosed receiving nonfinancial support from Astellas and Basilea.

GRANTED BREAKTHROUGH THERAPY DESIGNATION FOR IPF DURING FDA REVIEW9

Start your appropriate patients with IPF on OFEV

CONDUCT liver function tests (ALT, AST, and bilirubin) prior to initiating treatment with OFEV (nintedanib)

COMPLETE the OFEV Prescription Form—available at www.hcp.OFEV.com—and fax it to one of the participating specialty pharmacies listed on the form

OFFER enrollment in OPEN DOORS™, a patient support program for patients receiving OFEV

IMPORTANT SAFETY INFORMATION
ADVERSE REACTIONS
• Adverse reactions reported in ≥5% of OFEV patients included diarrhea, nausea, abdominal pain, liver enzyme elevation, vomiting, decreased appetite, weight decreased, headache, and hypertension.
• The most frequent serious adverse reactions reported in OFEV patients were bronchitis and myocardial infarction. The most common adverse events leading to death in OFEV patients versus placebo were pneumonia (0.7% vs. 0.6%), lung neoplasm malignant (0.3% vs. 0%), and myocardial infarction (0.3% vs. 0.2%). In the predefined category of major adverse cardiovascular events (MACE) including MI, fatal events were reported in 0.6% of OFEV versus 1.8% in placebo patients.

DRUG INTERACTIONS
• P-glycoprotein (P-gp) and CYP3A4 Inhibitors and Inducers: Coadministration with oral doses of a P-gp and CYP3A4 inducer, rifampicin, decreased exposure to nintedanib by 50%. Concomitant use of P-gp and CYP3A4 inducers (e.g., carbamazepine, phenytoin, and St. John’s wort) with OFEV should be avoided as these drugs may decrease exposure to nintedanib.
• Anticoagulants: Nintedanib may increase the risk of bleeding. Monitor patients on full anticoagulation therapy closely for bleeding and adjust anticoagulation treatment as necessary.

USE IN SPECIFIC POPULATIONS
• Nursing Mothers: Excretion of nintedanib and/or its metabolites into human milk is probable. Because of the potential for serious adverse reactions in nursing infants from OFEV, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
• Smokers: Smoking was associated with decreased exposure to OFEV, which may affect the efficacy of OFEV. Encourage patients to stop smoking prior to and during treatment.

Please see brief summary for OFEV on the following pages.

National Sarcoidosis Awareness Month

In conjunction with National Sarcoidosis Awareness Month in April, and in partnership with the Foundation for Sarcoidosis Research (FSR), the CHEST Foundation has launched the second annual Seek Answers. Inspire Results. campaign.

Throughout the campaign, the CHEST Foundation and FSR are offering tools for people with sarcoidosis and their caregivers. Among the materials in the provider and patient toolkits is the “Sarcofive,” a list of five questions designed to start proactive patient-doctor conversations and help people living with sarcoidosis to understand options and create a personalized plan to control their individual condition.

Additional campaign materials include a radio media tour, social media sharable images, infographics, and compelling digital assets, including a video and interactive, Web-based element. Further information can be found at chestnet.org/sarcoid.
Few pneumonia patients tested for HIV on admission

BY DOUG BRUNK
Pulmonary Medical News

SAN DIEGO – Only 39% of patients hospitalized for pneumonia underwent HIV testing, even though federal recommendations for universal HIV screening in all health care settings have been in place since 2006, according to the results of a retrospective, single-center study.

“Despite universal recommendations for HIV screening in all health care settings, HIV testing rates remain low among patients hospitalized with pneumonia,” Dr. Dana C. Clifton said at an annual scientific meeting on infectious diseases. “A number of patients were subsequently diagnosed with HIV after a prolonged delay.”

Of U.S. patients newly diagnosed with HIV, 41% report no prior HIV testing and an estimated 14%-25% of those living with HIV are undiagnosed, said Dr. Clifton, an internist at Duke University Medical Center, Durham, N.C. In 2006, the Centers for Disease Control and Prevention recommended routine HIV screening in all health care settings for all patients aged between 13 and 64 years old.

Dr. Clifton and her associates retrospectively evaluated patients admitted to Duke University Health System during 1996-2014 with a first primary diagnosis of pneumonia. They used ICD-9 codes for primary diagnosis of pneumonia at time of hospital admission, reviewed a subset of charts to validate the diagnosis, and conducted a random sample of those without prior HIV diagnosis to evaluate HIV testing. The primary outcome was HIV testing during pneumonia admission. Secondary outcomes were documented prior HIV testing in the electronic medical record and subsequent new HIV diagnosis following pneumonia admission.

During the time period studied, 6,858 patients, of which 345 (5%) were previously known to be HIV positive, were admitted with a primary diagnosis of pneumonia. 5,133 of the patients were discharged by general medicine or pulmonary service. Of the 6,513 not previously known to be HIV positive, 19 (0.3%) were diagnosed with HIV during hospital admission and 46 (0.7%) were diagnosed with HIV a median of 807 days after admission.

IDWeek marks the combined annual meetings of the Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, the HIV Medicine Association, and the Pediatric Infectious Diseases Society.

The researchers reported having no financial disclosures.

anticoagulation treatment as necessary [see Warnings and Precautions].

USE IN SPECIFIC POPULATIONS: Pregnancy: Pregnancy Category D. [See Warnings and Precautions]; OFEV (nintedanib) may cause fetal harm when administered to a pregnant woman. If OFEV is used during pregnancy, or if the patient becomes pregnant while taking OFEV, the patient should be apprised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with OFEV. In animal reproduction toxicology studies, nintedanib caused embryolethal deaths and teratogenic effects in rats and rabbits at less than and approximately 5 times the maximum recommended human dose (MRHD) in adults (on a plasma AUC basis at maternal oral doses of 2.5 and 15 mg/kg/day in rats and rabbits, respectively). Malformations included abnormalities in the vasculature, uronephric, and skeletal systems. Vasculature anomalies included missing or additional major blood vessels. Skeletal anomalies included abnormalities in the thoracic, lumbar, and caudal vertebrae (e.g., hemivertebra, missing, or asymmetrically ossified), ribs (bifid or fused), and stenotoma (fused, split, or unilaterally ossified). In some fetuses, organs in the urogenital system were missing.

In rabbits, a significant change in sex ratio was observed in fetuses; male/female ratio of approximately 7:1% to 29% at approximately 15 times the MRHD in adults (on an AUC basis at a maternal oral dose of 60 mg/kg/day). Nintedanib decreased post-natal viability of rat pups during the first 4 post-natal days when dams were exposed to less than the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day). Nursing Mothers: Nintedanib and its metabolites are excreted into the milk of lactating rats. Milk and plasma of lactating rats have similar concentrations of nintedanib and its metabolites. Excretion of nintedanib and plasma of lactating rats have similar concentrations of nintedanib and its metabolites. Excretion of nintedanib and its metabolites are excreted into the milk of lactating rats. Milk and plasma of lactating rats have similar concentrations of nintedanib and its metabolites. Excretion of nintedanib and its metabolites are excreted into the milk of lactating rats. Milk and plasma of lactating rats have similar concentrations of nintedanib and its metabolites. Excretion of nintedanib and plasma of lactating rats have similar concentrations of nintedanib and its metabolites.

decreased post-natal viability of rat pups during the first days after birth. In the single-dose study, less than 1% of the total dose of nintedanib is excreted via the kidney. Adjustment of dosage is appropriate or discontinuation of OFEV (nintedanib) as needed.

ADVISE patients not to make up for a missed dose or to discontinue OFEV while nursing. Nursing mothers: Nintedanib and its metabolites are excreted into the milk of lactating rats. Milk and plasma of lactating rats have similar concentrations of nintedanib and its metabolites. Excretion of nintedanib and its metabolites are excreted into the milk of lactating rats. Milk and plasma of lactating rats have similar concentrations of nintedanib and its metabolites. Excretion of nintedanib and its metabolites are excreted into the milk of lactating rats. Milk and plasma of lactating rats have similar concentrations of nintedanib and its metabolites. Excretion of nintedanib and its metabolites are excreted into the milk of lactating rats. Milk and plasma of lactating rats have similar concentrations of nintedanib and its metabolites.

Smokers: Smoking was associated with decreased exposure to OFEV, which may alter the effi cacy profile of OFEV. Encourage patients to stop smoking prior to treatment with OFEV and to avoid smoking when using OFEV.

OFEV (nintedanib) is not recommended for use in patients with mild hepatic impairment (Child Pugh B) and severe (Child Pugh C) hepatic impairment with OFEV is not recommended [see Warnings and Precautions]; Renal Impairment: Based on a single-dose study, less than 1% of the total dose of nintedanib is excreted via the kidney. Adjustment of the starting dose in patients with mild to moderate renal impairment is not required. The safety, effi cacy, and pharmacokinetics of nintedanib have not been studied in patients with severe renal impairment (>50 ml/min CrCl) and end-stage renal disease. Smokers: Smoking was associated with decreased exposure to OFEV, which may alter the effi cacy profile of OFEV. Encourage patients to stop smoking prior to treatment with OFEV and to avoid smoking when using OFEV.

OVERDOSAGE: In the trials, one patient was inadvertently exposed to a dose of 600 mg daily for a total of 21 days. A non-serious adverse event (nasopharyngitis) occurred and resolved during the period of incorrect dosing, with no onset of other reported events. Dose was also reported in two patients in oncology studies who were exposed to a maximum of 600 mg twice daily for up to 8 days. Adverse events reported were consistent with the existing safety profile of OFEV. Both patients recovered. In case of overdose, interrupt treatment and initiate general supportive measures as appropriate.

PATIENT COUNSELING INFORMATION: Advise the patient to read the FDA-approved patient labeling (Patient Information, FDA-Approved Prescribing Information) and the Patient Information leaflet before starting OFEV. Advise patients that they will need to undergo routine liver function testing periodically. Advise patients to immediately report any symptoms of a liver problem (e.g., skin or the whites 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]; Gastrointestinal Comorbidities: Inform patients that gastrointestinal disorders such as diarrhea, nausea, and vomiting were the most commonly reported gastrointestinal events occurring in patients who received OFEV (nintedanib). Advise patients that their healthcare provider may recommend hydration, anti-emetic medications (e.g., loperamide), or anti-emetic medications to treat these side effects. Temporary dosage reduction or discontinuation may be required. Instruct patients to contact their healthcare provider at the first signs of diarrhea or for any severe or persistent diarrhea, nausea, or vomiting [see Warnings and Precautions and Adverse Reactions]; Pregnancy: Counsel patients on pregnancy planning and prevention. Advise females of childbearing potential of the potential hazard to a fetus and to avoid becoming pregnant while receiving treatment with OFEV. Advise females of childbearing potential to notify their doctor if they become pregnant during therapy with OFEV [see Warnings and Precautions and Use in Specific Populations]; Adverse Thromboembolic Events: Advise patients about the signs and symptoms of acute myocardial ischemia and other arterial thromboembolic events and the urgency to seek immediate medical care for these conditions [see Warnings and Precautions]; Risk of Bleeding: Bleeding events have been reported. Advise smokers to stop smoking prior to treatment [see Warnings and Precautions]; Gastrointestinal Perforation: Serious gastrointestinal perforation events have been reported. Advise patients to report signs and symptoms of gastrointestinal perforation [see Warnings and Precautions]; Nursing Mothers: Advise patients to discontinue nursing when taking OFEV or discontinue OFEV while nursing [see Use in Specific Populations]; Smoking: Encourage patients to stop smoking prior to treatment with OFEV and to avoid smoking when using with OFEV. Administrate: Instruct patients to swallow OFEV capsules whole with liquid and not to chew or open the capsules due to the bitter taste. Advise patients to not make up for a missed dose [see Dosage and Administration].

Copyright © 2014 Boehringer Ingelheim International GmbH.

ALL RIGHTS RESERVED

OF-BS-10-14 (10-15) OF629900RPRD

R only

Boehringer Ingelheim

Routine screening is cost effective, compared with screening tests for colon cancer, diabetes, and breast cancer.

DR. CLIFTON

Few pneumonia patients tested for HIV on admission

BY DOUG BRUNK
Pulmonary Medical News

SAN DIEGO – Only 39% of patients hospitalized for pneumonia underwent HIV testing, even though federal recommendations for universal HIV screening in all health care settings have been in place since 2006, according to the results of a retrospective, single-center study.

“Despite universal recommendations for HIV screening in all health care settings, HIV testing rates remain low among patients hospitalized with pneumonia,” Dr. Dana C. Clifton said at an annual scientific meeting on infectious diseases. “A number of patients were subsequently diagnosed with HIV after a prolonged delay.”

Of U.S. patients newly diagnosed with HIV, 41% report no prior HIV testing and an estimated 14%-25% of those living with HIV are undiagnosed, said Dr. Clifton, an internist at Duke University Medical Center, Durham, N.C. In 2006, the Centers for Disease Control and Prevention recommended routine HIV screening in all health care settings for all patients aged between 13 and 64 years old.

Dr. Clifton and her associates retrospectively evaluated patients admitted to Duke University Health System during 1996-2014 with a first primary diagnosis of pneumonia. They used ICD-9 codes for primary diagnosis of pneumonia at time of hospital admission, reviewed a subset of charts to validate the diagnosis, and conducted a random sample of those without prior HIV diagnosis to evaluate HIV testing. The primary outcome was HIV testing during pneumonia admission. Secondary outcomes were documented prior HIV testing in the electronic medical record and subsequent new HIV diagnosis following pneumonia admission.

During the time period studied, 6,858 patients, of which 345 (5%) were previously known to be HIV positive, were admitted with a primary diagnosis of pneumonia. 5,133 of the patients were discharged by general medicine or pulmonary service. Of the 6,513 not previously known to be HIV positive, 19 (0.3%) were diagnosed with HIV during hospital admission and 46 (0.7%) were diagnosed with HIV a median of 807 days after admission.

IDWeek marks the combined annual meetings of the Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, the HIV Medicine Association, and the Pediatric Infectious Diseases Society.

The researchers reported having no financial disclosures.
Expiratory central airway collapse in 5% of smokers

BY MARY ANN MOON
Premier Medical News

Among current and former smokers with or without chronic obstructive pulmonary disease (COPD), expiratory central airway collapse develops in approximately 5% and is associated with a worse respiratory-related quality of life, greater dyspnea, and an increased rate of total and severe exacerbations of pulmonary problems, according to a report published online Feb. 2 in JAMA.

Until recently, expiratory central airway collapse (ECAC) could only be studied using bronchoscopy, so it was not very well characterized. For example, the estimated prevalence among patients with known respiratory problems ranged from 1% to 53%. With the increasing use of noninvasive imaging techniques, the condition is being recognized more often, especially in association with smoking and COPD, but it still remains poorly understood, said Dr. Surya P. Bhatt of the division of pulmonary, allergy, and critical care medicine, University of Alabama at Birmingham, and his associates.

To assess the prevalence and clinical significance of ECAC, the investigators analyzed paired CT images of inspiratory and expiratory scans collected in the multicenter COPDDGene study, focusing on scans for 8,820 current and former smokers aged 45-80 years (mean age, 59.7 years) who enrolled from local communities across the United States at 21 participating medical centers. Approximately 57% of the study participants were men, 66% were white and 34% were African American, 52% were active smokers, and 44% had COPD.

A total of 443 cases of ECAC were identified, for a prevalence of 5%.

ECAC was more common in participants with COPD (5.9%) than in those without COPD (4.3%), and the prevalence increased with increasing severity of COPD. Study subjects with ECAC were older than those without the condition. ECAC also was more frequent among women than men (7.2% vs 3.1%), and among whites than blacks (6.2% vs 2.5%). Participants with ECAC had a higher body-mass index, a higher prevalence of chronic bronchitis, and more pack-years of smoking than those without ECAC.

In the primary data analysis, adults with ECAC had a worse respiratory-related quality of life than those without the condition, as measured using the St. George’s Respiratory Questionnaire. This association remained robust, and was independent of the degree of airflow obstruction and the severity of COPD, after the data were adjusted to account for patient demographics, structural lung disease, and forced expiratory volume in 1 second. “We speculate that ECAC might explain some cases of dyspnea disproportionate to apparent obstructive airways disease measured by CT, spirometry, or both,” Dr. Bhatt and his associates said.

Participants with ECAC also had more severe dyspnea as measured by the modified Medical Research Council scale. ECAC was more frequent among women patients with COPD (5.9%) than in men (7.2% vs 3.1%), and among current and former smokers (44%) had COPD. Study subjects differed by race, gender, age, smoking status, and disease severity. Study participants were older (mean age, 59.7 years) who enrolled from local communities across the United States at 21 participating medical centers. Approximately 57% of the study participants were men, 66% were white and 34% were African American, 52% were active smokers, and 44% had COPD.

The prevalence of ECAC remained robust, and was independent of the degree of airflow obstruction and the severity of COPD, after the data were adjusted to account for patient demographics, structural lung disease, and forced expiratory volume in 1 second. “We speculate that ECAC might explain some cases of dyspnea disproportionate to apparent obstructive airways disease measured by CT, spirometry, or both,” Dr. Bhatt and his associates said.

Participants with ECAC also had more severe dyspnea as measured by the modified Medical Research Council scale. ECAC was more frequent among women (7.2% vs 3.1%) than men (5.9%), and in adults (7.2% vs 3.1%), and among current and former smokers (44%) had COPD. Study subjects differed by race, gender, age, smoking status, and disease severity. Study participants were older (mean age, 59.7 years) who enrolled from local communities across the United States at 21 participating medical centers. Approximately 57% of the study participants were men, 66% were white and 34% were African American, 52% were active smokers, and 44% had COPD.

The prevalence of ECAC remained robust, and was independent of the degree of airflow obstruction and the severity of COPD, after the data were adjusted to account for patient demographics, structural lung disease, and forced expiratory volume in 1 second. “We speculate that ECAC might explain some cases of dyspnea disproportionate to apparent obstructive airways disease measured by CT, spirometry, or both,” Dr. Bhatt and his associates said.

Participants with ECAC also had more severe dyspnea as measured by the modified Medical Research Council scale. ECAC was more frequent among women (7.2% vs 3.1%) than men (5.9%), and in adults (7.2% vs 3.1%), and among current and former smokers (44%) had COPD. Study subjects differed by race, gender, age, smoking status, and disease severity. Study participants were older (mean age, 59.7 years) who enrolled from local communities across the United States at 21 participating medical centers. Approximately 57% of the study participants were men, 66% were white and 34% were African American, 52% were active smokers, and 44% had COPD.
Continued from previous page

Council score (JAMA 2016 Feb 2. doi: 10.1001/jama.2015.19431). A subset of 7,456 study participants were assessed at 3 to 6-month intervals for a median of 4.3 years. Compared with participants who did not have ECAC, those who did develop more total exacerbations of pulmonary problems (35 vs. 58 events per 100 person-years) and more severe exacerbations requiring hospitalization (10 vs. 17 events per 100 person-years). Mortality, however, was not significantly different between children who had ECAC (9%) and those who did not (9.6%).

"Whether some of these [exacerbations] represent decompenated ECAC or whether ECAC is a marker for future severe respiratory events needs to be investigated. Our results sug-

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

Prevnar 13® is a suspension for intramuscular injection available in 0.5 mL single-dose prefilled syringes.

COMMENTS

More serious reactions (e.g., anaphylaxis) may accompany any component of Prevnar 13® or any diphtheria toxoid–containing vaccine.

A subset of 7,456 study participants were assessed at 3 to 6-month intervals for a median of 4.3 years. Compared with participants who did not have ECAC, those who did develop more total exacerbations of pulmonary problems (35 vs. 58 events per 100 person-years) and more severe exacerbations requiring hospitalization (10 vs. 17 events per 100 person-years). Mortality, however, was not significantly different between children who had ECAC (9%) and those who did not (9.6%).

"Whether some of these [exacerbations] represent decompenated ECAC or whether ECAC is a marker for future severe respiratory events needs to be investigated. Our results sug-

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

Prevnar 13® is a suspension for intramuscular injection available in 0.5 mL single-dose prefilled syringes.

COMMENTS

More serious reactions (e.g., anaphylaxis) may accompany any component of Prevnar 13® or any diphtheria toxoid–containing vaccine.
Interstitial lung abnormalities linked to high death risk

BY MARY ANN MOON
Frontline Medical News

In four large, separate research cohorts in which middle-aged and older participants underwent lung CT, interstitial lung abnormalities were associated with a higher-than-average risk of death within 3-9 years, according to a report published online in JAMA.

These imaging abnormalities were defined as specific patterns of increased lung density affecting more than 5% of any lung zone and included reticular or ground-glass abnormalities, diffuse centrilobular nodularity, nonemphysematous cysts, honeycombing, traction bronchiectasis, or pulmonary parenchymal architectural distortion diagnostic of fibrotic lung disease. They were identified in approximately 7% of the 11,691 study participants. The study findings, taken together with those of previous research, “demonstrate that despite often being undiagnosed and asymptomatic, interstitial lung abnormalities may be associated with lower survival rates among older persons,” said Dr. Rachael K. Putman of the pulmonary and critical care division at Brigham and Women’s Hospital and Harvard Medical School, Boston, and her associates.

Previously, interstitial lung abnormalities have been found in the same proportion, 7%, of the general population and have been associated with reduced lung capacity, exercise capacity, and gas exchange. The investigators hypothesized that “the presence of interstitial lung abnormalities would be associated with an increased rate of mortality.”

To test this hypothesis, they analyzed data from four large study cohorts that included lung CT: 2,633 participants in the Framingham Heart Study (median follow-up of 4 years after CT), 5,320 in the Age Gene/Environment Susceptibility (AGES)-Reykjavik study (median follow-up, 8.9 years), 2,068 in the Genetic Epidemiology of COPD (COPDGene) study (median follow-up, 6.5 years), and 1,670 participants in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study (median follow-up, 2.9 years).

The absolute rates of all-cause mortality were significantly higher among participants who had interstitial lung abnormalities than among those who did not. Mortality rates were 7% vs. 1% in the FHS, 56% vs. 33% in AGES-Reykjavik, 16% vs. 11% in COPDGene, and 11% vs. 5% in ECLIPSE. After the data were adjusted to account for confounding factors such as age, sex, race, body-mass index, current smoking status, and pack-years of smoking, the lung abnormalities remained strongly associated with a higher risk of death in the FHS (hazard ratio, 2.7), AGES-Reykjavik (HR, 1.3), COPDGene (HR, 1.8), and ECLIPSE (HR, 1.4) studies.

The association remained robust in further analyses restricted only to nonsmoking participants, Dr. Putman and her associates said (JAMA. 2016 Feb 16;315[7]:672-81. doi: 10.1001/jama.2016.0518).

The AGES-Reykjavik study was the only one to assess causes of death. In that cohort, participants who had interstitial lung abnormalities were more likely to die of a respiratory cause (13%) than were those who had no such abnormalities (4%) or those who had indeterminate findings on lung CT (6%). After the data were adjusted to account for confounding factors, participants with interstitial lung abnormalities were at much higher risk of dying from a respiratory cause (OR, 2.4) such as respiratory failure or pulmonary fibrosis.

This study was supported by the National Institutes of Health; the Icelandic Research Fund; the Lanspitali Scientific Fund; the National Cancer Institute; the National Heart, Lung, and Blood Institute; GlaxoSmithKline; the National Institute on Aging; the Icelandic Heart Association; and the Icelandic Parliament. Dr. Putman reported having no relevant financial disclosures; her associates reported numerous ties to industry sources.

COPD exacerbation amps up stroke risk

BY NICOLA GARRETT
Frontline Medical News

People with chronic obstructive pulmonary disease have an approximately 20% increased risk of stroke, and the risk is highest during the time after an acute exacerbation of COPD, data from a large epidemiologic study indicate.

The study also indicated that cigarette smoking was a strong risk factor for stroke and that hypertension management is important in COPD patients given the elevated risk for hemorrhagic strokes observed, according to Dr. Marileen L. P. Portegies of Erasmus MC University Medical Center, Rotterdam, the Netherlands, and her colleagues.

In 13,115 participants from the Rotterdam study, people with COPD had a 6.7-fold increase in the risk of stroke within the first 7 weeks of a severe exacerbation (hazard ratio, 6.66; 95% confidence interval, 2.42-18.20).

The study (Am J Respir Crit Care Med. 2016;193:251-8) found that 1,250 of the participants had a stroke (701 were ischemic and 107 hemorrhagic) over 126,347 person-years of follow-up.

After researchers adjusted for age and sex, COPD was significantly associated with all stroke (HR, 1.20), ischemic stroke (HR, 1.27), and hemorrhagic stroke (HR, 1.70).

Smoking was the strongest explanatory factor for the association between COPD and stroke, the researchers said. Adjustments for cardiovascular risk factors gave similar effect sizes, whereas adjustments for smoking attenuated the effect sizes: for all stroke, (HR, 1.09); for ischemic stroke, (HR, 1.13); and for hemorrhagic stroke, (HR 1.53).

“Our study reveals the importance of smoking as a shared risk factor and implicates that clinicians should be aware of the higher risk of both stroke subtypes in subjects with COPD, especially after severe exacerbations,” they concluded. Smoking failed to account for the period of a COPD exacerbation during which risk for strokes and MIs increase.
Survey finds inconsistencies in delirium screening

BY KARI OAKES
Frontline Medical News

ORLANDO – Most of the ICU directors responding to a survey had delirium screening protocols in place, but said their current practices don’t conform to best practice guidelines.

“While most ICUs have protocols that incorporate delirium screening with a validated tool, most perceived current delirium prevention and treatment strategies do not reflect best evidence or current pain, agitation, and delirium practice guidelines,” senior author Amy Dzierba, Pharm.D., said in an interview. Practice guidelines for pain, agitation, and delirium in the ICU, promulgated jointly by the American College of Critical Care Medicine (ACCM) and the Society of Critical Care Medicine (SCCM) in 2013, call for ICU patients to be screened regularly for delirium, and recommend non-pharmacologic and pharmacologic interventions to prevent, or reduce the duration of, delirium in critically ill adults.

The Critical Care Pharmacy Trials Network (CCPTN) initiated the survey. Responses came from 19 hospitals with 42 ICUs, with 74% of them being academic medical centers and the remainder teaching community hospitals. Joshua Swan, Pharm.D. of Texas Southern University, Houston, presented the study findings at the Society for Critical Care Medicine’s annual Critical Care Congress.

The multicenter, observational, cross-sectional study used a validated, web-based survey that included questions about demographic characteristics of the ICUs, as well as a series of 36 questions about perceptions of delirium screening, prevention, and treatment practices.

Most ICUs (26/42, 62%) used the Confusion Assessment Method for the ICU (CAM-ICU), while another 10 hospitals (24%) used the Intensive Care Delirium Screening Checklist Worksheet (ICDSC). The other hospitals used physician or nurse opinion, or another method.

Twenty-two of 42 respondents (58%) judged that they screened for delirium twice daily; 10 ICUs thought they screened three times daily, three screened once daily, and the rest thought they screened more frequently than twice daily.

A non-pharmacologic delirium prevention and reduction protocol was in place for 33 (80%) of the ICUs. Specific interventions that respondents judged they used, regardless of delirium presence, included reorientation in more than 80% of ICUs, catheter and restraint removal in more than 70% of ICUs responding, and ensuring eyeglasses were donned for about 70% of ICUs.

Less frequently-used interventions were provision of hearing aids, early mobilization, reduction of unnecessary noise and stimulation, music therapy, provision of earplugs, and cognitive exercises. About half of survey respondents said that their ICUs used early mobilization as a delirium prevention strategy.

Perceived pharmacologic strategies that were used in about half of the ICUs for patients without delirium included avoidance of benzodiazepines for sedation, minimization of anticholinergic medication, and minimization of caffeine.

“Future studies should compare actual practices to those that are perceived,” said Dr. Dzierba, clinical pharmacy manager for adult critical care at Columbia University Medical Center’s New York-Presbyterian Hospital. Dr. Dzierba reported no external source of funding for the study, and the authors had no relevant conflicts of interest to disclose.

koakes@frontlinemedcom.com

On Twitter @karioakes
Tool forecasts performance at 1 year after ICU stay

BY KARI OAKES
Frontline Medical News

ORLANDO – A new clinical prediction rule correlates well with performance status at 1 year after ICU hospitalization in patients over age 80.

Illness severity, comorbidities, baseline frailty, a primary diagnosis of stroke, and being male were all predictors of poor performance status at 1 year. A primary diagnosis of emergency coronary artery bypass grafting or valve replacement, a high baseline performance status, and being married were associated with good performance status at 1 year.

The e-statistic for the model, a standard indicator of predictive power, was 0.811, a figure that indicates good predictive ability.

The findings from the REALISTIC 80 (Realities, Expectations, and Attitudes to Life Support Technologies in Intensive Care for Octogenarians) study of 17 patient and illness characteristics allowed Dr. Daren Heyland, professor of medicine and epidemiology at Queen’s University, Kingston, Ont., and his coinvestigators in the Canadian Critical Care Trials Group (CCCTG), to conclude that eight factors were most predictive of performance status at 12 months for ICU patients aged 80 and over. REALISTIC 80 is a CCCTG project.

The values for the predictors are derived from responses to an online guided questionnaire called the ICU Workbook. The questionnaire is completed by patients’ family members or surrogates, and the responses are used to calculate the values that constitute the clinical prediction rule’s components.

Gathering this information may help health care providers and family members in end-of-life decision making, said Dr. Heyland, who is also director of CARENET, which hosts the online guided questionnaire and is an affiliation of Canadian researchers focused on end-of-life care. He spoke at the Society of Critical Care Medicine’s Critical Care Congress.

“For the very elderly, it is plausible that poor communication and decision making lead to overutilization of ICU resources and poor-quality end-of-life care,” he said.

REALISTIC 80 enrolled 434 patients, aged 80-100 years (mean age, 84.6) who were admitted to ICUs at participating institutions. The primary outcome measure of REALISTIC 80 was the 12-month survival and health-related quality of life; “recovery from critical illness” was defined as a Palliative Performance Scale (PPS) score of greater than or equal to 60% at 12 months.

Patients scoring at 60% on the 0%-100% scale of this functional status measure may have reduced ambulation, be unable to engage in housework or hobbies, have significant disease, need assistance, and be confused at times. An advantage of this scale, said Dr. Heyland, is that it eliminates survivorship bias in analyzing data, since a score of 0 is assigned to individuals who die.

About 50% of patients had died by 12 months; about 21% were alive, with a reduced health status below the threshold of 60 on the PPS; and about 29% were alive, with a PPS score above the predetermined quality of life threshold.

About 17% of participants were lost to follow-up. The predictive model was derived from completed cases, and a sensitivity analysis using imputed data for missing patients showed that it retained its predictive value.

Dr. Heyland said the presence of advance directives didn’t appear to affect outcomes.

Dying in the ICU after days of mechanical ventilation or surviving with very low performance status “doesn’t sound like good quality of life to me, and it illustrates the challenge we have as clinicians in getting to what’s best for patients,” he said.

The study was funded by the Canadian Institutes of Health Research and conducted under the auspices of the CCCTG and CARENET. The study investigators reported no other relevant financial disclosures.

Ebola patients treated in the West showed 81.5% survival

BY MARY ANN MOON
Frontline Medical News

Overall survival was 81.5% for the 27 patients with Ebola virus infection who were treated in the United States or Europe during the recent outbreak, according to a report published online Feb. 18 in the New England Journal of Medicine.

This is markedly higher than the 37%-74% survival reported for the almost 29,000 cases treated in West Africa, where treatment centers were challenged by overwhelming numbers of critically ill patients; limited medical supplies; insufficient numbers of caregivers; limited water, electricity, refrigeration, and other basic resources; and hot, humid working conditions that reduced the time health care personnel could attend to patients while wearing the required protective gear, said Dr. Timothy M. Uyeki of the Centers for Disease Control and Prevention, Atlanta, and his associates.

The investigators performed a retrospective analysis of the medical records of these 27 patients in a descriptive study of their clinical care. The patients were treated from August 2014 through December 2015 at 15 hospitals in 9 countries. Twenty (74%) were medically evacuated from West Africa, three (11%) were Western health care personnel who acquired the disease while caring for patients, and four were “imported” patients who contracted the virus while in West Africa but didn’t become ill until after they traveled to the United States or Europe. Overall, 22 of the patients (81%) were health care personnel, of whom 17 (77%) contracted the virus in West Africa.

Overall mortality was 11.1% after 2 weeks of illness and 18.5% after 4 weeks. The five patients who died were all aged 42 years or older and were significantly older than those who survived. Being 40-45 years old or older has been identified as a risk factor in West Africa as well.

Those who died also were hospitalized significantly later after the onset of illness. At least six more patients would have died if they hadn’t received advanced organ support: two required noninvasive ventilation, two required invasive mechanical ventilation, and two required both invasive mechanical ventilation and continuous renal-replacement therapy.

Routine therapies included oral or intravenous fluid replacement, total parenteral nutrition, antiemetics, empirical treatment with multiple antibiotics, nonconvalescent blood products, and respiratory supportive care. Most patients also received investigative therapies such as monoclonal antibody cocktails, antivirals, and treatments aimed at counteracting vascular leakage.

A wide range of possible adverse effects were reported — including systemic inflammatory response syndrome, hypotension, elevated aminotransferase levels, and transfusion-associated acute lung injury — but couldn’t be distinguished from the effects of supportive treatments or even of the virus itself.

“Because of their uncontrolled administration and because most patients received multiple, overlapping investigative therapies,” the researchers said (N Engl J Med. 2016 Feb 18;374:636-46. doi: 10.1056/NEJMoA1504874).

“One key feature” of the lifesaving clinical care was laboratory testing to closely monitor electrolyte levels and hematologic factors.

“Our experience suggests that early presentation and receipt of supportive care, IV fluid resuscitation, careful fluid management and electrolyte replacement to correct metabolic abnormalities, nutritional support, and critical care support may reduce mortality among patients with Ebola virus disease,” Dr. Uyeki and his associates said.

Eight (30%) of the patients in this study presented with cough and nine required ventilatory assistance, and difficulty breathing raised the risk of death.

They noted that, until now, the Ebola virus infection was not thought to involve a clinically significant respiratory component, and that the “pathophysiologically mechanism of pulmonary disease in patients with Ebola virus infection is unknown.”

This study was supported by the working group of the U.S.–European Clinical Network on Clinical Management of Ebola Virus Disease Patients in the U.S. and Europe. Dr. Uyeki reported having no relevant financial disclosures; two of his associates reported ties to Epiguard and Pfizer.
Periop statins don’t avert acute kidney injury

BY KARI OAKES
Frontline Medical News

ORLANDO – Statins administered perioperatively offered no protection against acute kidney injury following cardiac surgery, according to new results of a 5-year randomized clinical trial. The findings held true whether or not patients were naive to statins; serum creatinine levels actually increased significantly more for statin-naive patients given atorvastatin than those given placebo.

Dr. Billings: Continuing or withdrawing statin treatment doesn’t affect AKI.

The study was stopped early for patients naive to statins because increased acute kidney injury was seen in those patients who had chronic kidney disease (eGFR less than 60 mL/min/1.73 m²), and was subsequently stopped early for futility for all patients.

“De novo initiation of daily perioperative atorvastatin treatment did not reduce the incidence of AKI or reduce the increase in serum creatinine concentration associated with cardiac surgery,” wrote Dr. Frederic T. Billings IV, professor of medicine at Vanderbilt University, Nashville, Tenn., and his collaborators. The findings (JAMA 2016 Feb 23. doi: 10.1001/jama.2016.0548) were published concurrently with his presentation at the Critical Care Congress, sponsored by the Society of Critical Care Medicine.

In what Dr. Phil B. Fontanarosa, executive editor of JAMA and co-moderator of the late-breaking trials session at the meeting, described as “really an elegant clinical trial,” Dr. Billings and his collaborators enrolled 615 patients over 5 years at Vanderbilt University Medical Center. Patients undergoing elective coronary artery bypass grafting, valvular heart surgery, or ascending aortic surgery were eligible. Patients were excluded if they had prior statin intolerance, acute coronary syndrome, or liver dysfunction; were taking potent CYP3A4 inhibitors or cyclosporine; were receiving renal replacement therapy or had a kidney transplant; or were pregnant.

Both patients currently on a statin and patients naive to statins were recruited. Statin-naive patients received 80 mg atorvastatin the day before surgery, and then 40 mg of atorvastatin on the day of surgery and daily following surgery, or a matched placebo regimen.

Patients who were already on a statin received the study drug only on days that they would not have
received a statin if treated according to the current standard of care. It was deemed unethical to allow those patients to receive placebo during and after surgery, since observational studies suggested that doing so might increase their potential for AKI.

For those patients already on a statin, this meant that they stayed on their usual regimen until the day of surgery, and then were randomized to receive either 80 mg of atorvastatin on the day of surgery and 40 mg of atorvastatin the day after surgery, or a matching placebo regimen.

For both groups, the study drug was given at least 3 hours before surgery on the day of surgery.

Randomization was stratified for prior statin use, for chronic kidney disease, and by history of diabetes. The 199 patients naïve to statins and the 416 already on a statin were similar in demographic and health characteristics. Median age was 67 years, 188 (30.6%) were women; 202 participants (32.8%) had diabetes.

The primary outcome measure was diagnosis of AKI, defined as an increase of 0.3 mg/dL in serum creatinine, or beginning renal replacement therapy within 48 hours of surgery. Baseline serum creatinine was measured no more than 7 days prior to surgery.

Continued on following page
Continued from previous page

AKI occurred in 64 of 308 patients (20.8%) in the atorvastatin group, and in 60 of 307 patients (19.5%) receiving placebo overall (P = .75). For those naive to statins, 21.6% of the atorvastatin group and 13.4% of the placebo group developed AKI (P = .15). Overall, 179 enrolled patients had CKD, and the incidence of AKI did not significantly differ in the atorvastatin and the placebo arms of this subgroup.

The subpopulation of participants with CKD who were statin naïve (n = 36) saw an increased incidence of AKI with atorvastatin compared to placebo. AKI occurred in 9 of 17 patients (52.9%) given atorvastatin, and in 3 of 19 (15.8%) given placebo group (RR, 3.35 [95% confidence interval 1.02 to 10.05]; P = .03). “It should be noted that the number of patients in this subgroup was particularly small, leading to a wide confidence interval and an increased chance of type I error,” said Dr. Billings.

Secondary outcome measures were maximum increase in creatinine concentration from baseline through postop day 2, delirium in the ICU, degree of myocardial injury, and incidence of postoperative pneumonia, atrial fibrillation, or stroke. Perioper-
Advances in interdisciplinary research have demonstrated that atorvastatin administration did not affect any of these endpoints. The safety analysis showed no indications of increased risk of skeletal muscle or liver injury with perioperative atorvastatin use.

In the real world, “Most patients presenting for cardiac surgery ... are already taking statins, and in the current study there was little evidence that continuation or withdrawal from statin treatment on the day of surgery and postoperative day 1 affects AKI,” wrote Dr. Billings and his co-authors.

Study limitations included its single-center design, and the use of AKI criteria that may not be sensitive to late-developing AKI. Also, for enrolled patients who were already on statin, statin exposure was not reduced in comparison with usual care. The National Institutes of Health and the Vanderbilt University Medical Center department of anesthesiology funded the study. Dr. Brown reported receiving grants from Shire Pharmaceuticals and New Haven Pharmaceuticals, and personal fees from Novartis Pharmaceuticals and Alnylam Pharmaceuticals. The other authors reported no conflicts of interest.

FDA approves new anthrax treatment

The Food and Drug Administration has approved Anthim (obitoclaximab) injection to treat inhalational anthrax, in combination with appropriate antibacterial drugs.

Anthim is a monoclonal antibody that neutralizes toxins produced by the bacterium Bacillus anthracis. Anthim was approved under the FDA’s Animal Rule, which allows efficacy findings from adequate and well-controlled animal studies to support FDA approval when it is not feasible or ethical to conduct efficacy trials in humans. When alternative therapies are not available or not appropriate, anthim can be used to prevent inhalational anthrax, a rare disease that can occur after exposure to infected animals or contaminated animal products, or as a result of an intentional release of anthrax spores.

The drug was developed by Elusys Therapeutics Inc. of Pine Brook, N.J., in conjunction with the U.S. Department of Health and Human Services’ Biomedical Advanced Research and Development Authority. Anthim’s effectiveness was demonstrated in studies conducted in animals based on survival at the end of the studies. More animals treated with Anthim lived, compared with animals treated with placebo. Anthim administered in combination with antibacterial drugs resulted in higher survival outcomes than any antibacterial therapy alone.

The safety of Anthim was evaluated in 320 healthy human volunteers. The most frequently reported side effects were headache, itching (pruritus), upper respiratory tract infections, cough, nasal congestion, hives, and bruising, swelling and pain at the infusion site.

For more information, see the FDA’s approval announcement.
I n patients with new-onset hypertension and obstructive sleep apnea, continuous positive airway pressure (CPAP) therapy plus antihypertensive treatment with losartan led to reductions in systolic blood pressure beyond those achieved with losartan alone, a two-phase study found.

"Adding CPAP treatment to losartan may reduce blood pressure in a clinically relevant way if the patients are compliant with the device," said Dr. Erik Thunström of the Sahlgrenska Academy at the University of Gothenburg, Sweden, and his associates. If using CPAP with losartan has an additive blood pressure-lowering effect, it "favors the idea that it contributes to a further down-regulation of RAAS [renin-angiotensin-aldosterone system] activity in new-onset hypertension and OSA".

In their open-label study, 89 men and women with new-onset untreated hypertension – 54 of whom were found to have obstructive sleep apnea (OSA) through a home sleep study and 35 of whom were determined to not have OSA – were treated for 6 weeks with losartan, 50 mg daily. Ambulatory 24-hour blood pressure monitoring was performed before and after treatment. The patients with OSA were then randomized to receive 6 weeks of nightly add-on CPAP therapy or to continue losartan alone. Ambulatory 24-hour blood pressure monitoring was performed again. Losartan alone reduced blood pressure in patients with hypertension and concomitant OSA, but the effect was smaller than that seen in patients without OSA. Statistically significant differences were seen in the mean net reduction in morning systolic blood pressure and morning mean arterial pressure. After 6 weeks of losartan alone, a blood pressure less than 130/80 mm Hg was achieved by 12.5% of the patients with OSA and by 29% of the patients without OSA. After 6 weeks of add-on CPAP therapy, 25% of patients with OSA achieved blood pressures less than 130/80 mm Hg. The differences in blood pressures for the OSA patients receiving CPAP plus losartan and those receiving losartan alone were 4.4 mm Hg for 24-hour systolic blood pressure, 1.9 mm Hg for diastolic, and 2.5 mm Hg for mean arterial pressure.

The most "robust" blood pressure changes were seen in the patients who used CPAP therapy for more than 4 hours every night, reducing the mean 24-hour systolic blood pressure by 6.5 mm Hg, the diastolic pressure by 3.8 mm Hg, and the mean arterial blood pressure by 4.6 mm Hg, the researchers reported (Ann J Respir Crit Care Med. 2016 Feb;193:310-20). "Adding CPAP to treatment with losartan reduced the mean 24-hour systolic blood pressure by 6.5 mm Hg in the subgroup of patients with OSA who were adherent with CPAP," they wrote.

Dr. David Schulman, FCCP, comments: The relationship between sleep apnea and hypertension (both prevalent and incident) has been well described for many years. It is not entirely clear, however, that treatment of obstructive sleep apnea can lead to a meaningful decrease in blood pressure. Although relatively small, this study by Thunstrom et al sheds some additional light on the association. Patients with hypertension and comorbid obstructive sleep apnea (OSA) were less likely to show a meaningful response to antihypertensives than those without concomitant sleep-disordered breathing. In the subgroup with OSA that was randomized to subsequent administration of CPAP, blood pressure dropped more than it did with antihypertensive alone, albeit by only 4 mm Hg (and slightly more in the highly CPAP adherent subjects).

There are a couple of interesting features regarding subject enrollment that are worthy of mention. First, the study was restricted to individuals with a body mass index below 35, potentially limiting generalizability of the findings to a more obese population. Importantly, though, all subjects were screened for OSA, independent of sleepiness, suggesting that the findings may be extrapolated to non-sleepy apneics, a population that we are probably not as aggressive about identifying. Will this manuscript change current practice? Probably not. But it may offer some insight into the mechanism by which sleep apnea increases blood pressure. And if it leads more providers to screen even their non-sleepy hypertensives for sleep-disordered breathing in the hope of improving future cardiovascular risk, that would be a breath of fresh air.

Sleep apnea found in 57% of veterans with PTSD

O bstructive sleep apnea syndrome (OSAS) was diagnosed in more than half of 200 active duty service members with combat-related post-traumatic stress disorder (PTSD) who were studied at Walter Reed Army Medical Center in Washington. Compared with age-matched peers with just one of these disorders, the service members with PTSD and OSAS had poorer somnolence and sleep-related quality of life and were less adherent and responsive to positive airway pressure therapy.

The findings “highlight the need for a high index of suspicion and a comprehensive approach to identifying and treating sleep-disordered breathing in these patients,” Dr. Christopher J. Lettieri of the Uniformed Services University in Bethesda, Md., and his associates wrote (Chest. 2016 Feb;149[2]:483-90). “Given the prevalence of OSAS in patients with PTSD and its adverse impact on symptoms and adherence, early identification may improve outcomes.”

In the observational cohort study, 200 consecutive active duty service members who were diagnosed with PTSD as part of post-deployment screening underwent sleep evaluations regardless of whether there was clinical suspicion of sleep-disordered breathing. More than half – about 57% – were diagnosed with OSAS. Almost 60% of the study group had mild traumatic brain injury, which has been connected in prior research to sleep-disordered breathing and many had comorbid insomnia. Those who were diagnosed with OSAS were older and had higher BMIs than those not found to have OSAS. All 200 patients were compared with 50 consecutive age-matched control patients who had OSAS but had not been deployed and did not have PTSD, as well as with 50 age-matched service members without prior deployment or either of the two disorders. All of the patients diagnosed with OSAS were prescribed positive airway pressure (PAP) therapy and evaluated after a month.

Sleep quality was poor in the majority of patients with PTSD, and OSAS and PTSD were both independently associated with increased daytime sleepiness and lower quality-of-life index scores. However, patients with both conditions fared significantly worse, particularly with respect to quality of life as measured by the Functional Outcomes of Sleep Questionnaire (FOSQ). FOSQ scores were abnormal at baseline in 60% of those with PTSD and OSAS, 43% with PTSD alone, 24% with OSAS alone, and 7% of those with neither condition.

While continuous PAP therapy improved daytime sleepiness and quality of life in patients with both PTSD and OSAS, the degree of improvement was less than that experienced by those with OSAS alone. PTSD “represents an independent barrier to the effective treatment of OSAS and should prompt multipronged and individualized care,” they wrote.

The researchers reported having no financial disclosures.

CPAP extended BP-lowering impact of losartan

BY CHRISTINE KILGORE
Frontline Medical News

SLEEP MEDICINE APRIL 2016 • CHEST PHYSICIAN
$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

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.
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
 Certain cancers raise the risk for subsequent NSCLC

BY DOUG BRUNK
Frontline Medical News

PHOENIX – A history of head and neck, lung, bladder, and hematologic malignancies was associated with an increased rate of subsequent non–small cell lung cancer (NSCLC), a large analysis of national data found.

“It is unclear to what extent the higher rate of primary NSCLC in these patients may be attributed to smoking, previous cancer history, or other lung cancer risk factors,” researchers led by Dr. Geena Wu wrote in an abstract presented during a poster session at the annual meeting of the Society of Thoracic Surgeons. “Further research using individual smoking data may better delineate who is at increased risk of NSCLC based on prior cancer site and smoking history.”

In a study that Dr. Wu led during a research fellowship at the City of Hope National Medical Center, Duarte, Calif., she and her associates used the Surveillance, Epidemiology, and End Results (SEER) 1992-2007 dataset to identify 32,058 patients with a prior malignancy who subsequently developed primary lung cancer at 6 months or more after their initial cancer. They calculated standardized incidence ratios (SIRs) for NSCLC as a rate of observed to expected NSCLC cases adjusted by person-years at risk, age, gender, and time of diagnosis.

The researchers found that patients with a history of the following cancers had higher rates of second primary NSCLC than expected: head and neck (SIR, 4.00), colon and rectum (SIR, 1.16), pancreas (SIR, 1.44), lung (SIR, 4.88), bladder (SIR, 1.97), kidney (SIR, 1.21), breast (SIR, 1.09), and leukemia or lymphoma (SIR, 1.40).

At the same time, patients with a history of pancreatic or breast cancer who were treated with radiation had a higher incidence of second primary NSCLC (SIR of 2.54 and SIR of 1.14, respectively), while those who were not treated with radiation did not.

“Just because someone has a previous history of cancer, they’re not necessarily at increased risk of a second lung cancer,” Dr. Wu, who is now a fourth-year general surgery resident at Maricopa County Hospital in Phoenix said in an interview at the meeting. “You have to look at what kind of cancer they had and what their smoking history is – whether or not they continue to smoke, because smoking is such an important risk factor.”

The SEER database does not contain information about patient smoking history. It also lacks details about the type of chemotherapy patients receive, “so whether or not chemotherapy plays an impact in the elevated risk of lung cancer we can’t say.”

Dr. Wu reported having no financial disclosures.

dbrunk@frontlinemedcom.com
SELECTED IMPORTANT SAFETY INFORMATION

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA

(A) Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. If anticoagulation with ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

(B) Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:
- use of indwelling epidural catheters
- concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants
- a history of traumatic or repeated epidural or spinal punctures
- a history of spinal deformity or spinal surgery
- optimal timing between the administration of ELIQUIS and neuraxial procedures is not known

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated.

CONTRAINDICATIONS
- Active pathological bleeding
- Severe hypersensitivity reaction to ELIQUIS (e.g., anaphylactic reactions)

WARNINGS AND PRECAUTIONS

Increased Risk of Thrombotic Events After Premature Discontinuation: Premature discontinuation of any oral anticoagulant, including ELIQUIS, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

Bleeding Risk: ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.
- Concomitant use of drugs affecting hemostasis increases the risk of bleeding, including aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, SSRIs, SNRIs, and NSAIDs.
- Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage.
- There is no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist for at least 24 hours after the last dose (i.e., about two half-lives). A specific antidote for ELIQUIS is not available.

- Spinal/Epidural Anesthesia or Puncture: Patients treated with ELIQUIS undergoing spinal epidural anesthesia or puncture may develop an epidural or spinal hematoma which can result in long-term or permanent paralysis. The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS. The next dose of ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours.

Monitor patients frequently and if neurological compromise is noted, urgent diagnosis and treatment is necessary. Physicians should consider the potential benefit versus the risk of neuraxial intervention in ELIQUIS patients.

- Prosthetic Heart Valves: The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves and is not recommended in these patients.

- Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy: Initiation of ELIQUIS is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

ADVERSE REACTIONS
- The most common and most serious adverse reactions reported with ELIQUIS were related to bleeding.

TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS
- ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be noncritical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established.

DRUG INTERACTIONS
- **Strong Dual Inhibitors of CYP3A4 and P-gp:** Inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) increase exposure to apixaban and increase the risk of bleeding. For patients receiving ELIQUIS doses of 5 mg or 10 mg twice daily, reduce the dose of ELIQUIS by 50% when ELIQUIS is coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin). In patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS with strong dual inhibitors of CYP3A4 and P-gp.
- **Strong Dual Inducers of CYP3A4 and P-gp:** Avoid concomitant use of ELIQUIS with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John’s wort) because such drugs will decrease exposure to apixaban and increase the risk of stroke and other thromboembolic events.
Approved for 6 indications

Treatment of PE

Reduction in risk of stroke/systemic embolism in NVAF

Prophylaxis of DVT, which may lead to PE, after hip replacement surgery

Prophylaxis of DVT, which may lead to PE, after knee replacement surgery

Treatment of DVT

Reduction in the risk of recurrent DVT and PE following initial therapy

Learn more about ELIQUIS for the treatment of DVT/PE and access reprints of our clinical studies.

hcp.eliquis.com

NVAF=nonvalvular atrial fibrillation; DVT=deep vein thrombosis; PE=pulmonary embolism.

SELECTED IMPORTANT SAFETY INFORMATION (CONT’D)

DRUG INTERACTIONS (CONT’D)

• Anticoagulants and Antiplatelet Agents: Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding. APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo.

PREGNANCY CATEGORY B

• There are no adequate and well-controlled studies of ELIQUIS in pregnant women. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. ELIQUIS should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Please see Brief Summary of Full Prescribing Information, including Boxed WARNINGS, on the adjacent pages.
INDICATIONS AND USAGE

There is no established way to reverse the anticoagulant effect of apixaban, which can be expected in the emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage.

- Severe hypersensitivity reaction to ELIQUIS (e.g., anaphylactic reactions) [see Warnings and Precautions and Adverse Reactions]
- Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events after premature discontinuation
- Bleeding in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE and AVERROES

CONTRAINDICATIONS

ELIQUIS is contraindicated in patients with the following conditions:

- Active pathological bleeding [see Warnings and Precautions and Adverse Reactions]
- Severe hypersensitivity reaction to ELIQUIS (e.g., anaphylactic reactions) [see Adverse Reactions]

DOSE AND ADMINISTRATION (Selected information)

Temporary Interruption for Surgery and Other Interventions

ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding where the bleeding would not be critical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established. (For complete Dosage and Administration section, see full Prescribing Information.)

WARNING: Premature Discontinuation of ELIQUIS Increases the Risk of Thrombotic Events

When neuraxial anesthesia (spinal/epidural anesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing epidural or spinal hematoma which can result in long-term or permanent paralysis. The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS (apixaban). The next dose of ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours.

Monitor patients frequently for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, bowel, or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

Patients with Prosthetic Heart Valves

The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves. Therefore, use of ELIQUIS is not recommended in these patients.

Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy

Initiation of ELIQUIS is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the prescribing information.

- Increased risk of thrombotic events after premature discontinuation
- Bleeding [see Warnings and Precautions]
- Spinal/epidural anesthesia or puncture [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.

Reduction of Risk of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation

The safety of ELIQUIS was evaluated in the ARISTOTLE and AVERROES studies (see Clinical Studies (14) in full Prescribing Information), including 11,284 patients exposed to ELIQUIS 5 mg twice daily and 602 patients exposed to ELIQUIS 2.5 mg twice daily. The duration of ELIQUIS exposure was ≥12 months for 9375 patients and ≥24 months for 3369 patients in the two studies. In ARISTOTLE, the mean duration of exposure was 89 weeks (≈15,000 patient-years). In AVERROES, the mean duration of exposure was approximately 59 weeks (≈3000 patient-years). The most common reason for treatment discontinuation in both studies was for bleeding-related adverse reactions; in ARISTOTLE this occurred in 1.7% and 2.5% of patients treated with ELIQUIS and warfarin, respectively, and in AVERROES, in 1.5% and 1.3% on ELIQUIS and aspirin, respectively.

Bleeding in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE and AVERROES

Table 1 shows the number of patients experiencing major bleeding during the treatment period and bleeding rate (percentage of subjects with at least one bleeding event per 100 patient-years) in ARISTOTLE and AVERROES.

Table 1: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE

<table>
<thead>
<tr>
<th>Bleeding Event</th>
<th>ELIQUIS N=9088</th>
<th>Warfarin N=9052</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>327 (2.13)</td>
<td>462 (2.09)</td>
<td>0.89 (0.60, 0.80)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Intracranial (ICH)</td>
<td>52 (0.33)</td>
<td>125 (0.82)</td>
<td>0.41 (0.30, 0.57)</td>
<td>-</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>38 (0.24)</td>
<td>74 (0.49)</td>
<td>0.51 (0.34, 0.75)</td>
<td>-</td>
</tr>
<tr>
<td>Other ICH</td>
<td>15 (0.10)</td>
<td>51 (0.34)</td>
<td>0.29 (0.16, 0.51)</td>
<td>-</td>
</tr>
<tr>
<td>Gastrointestinal (GI)</td>
<td>128 (0.83)</td>
<td>141 (0.93)</td>
<td>0.89 (0.70, 1.14)</td>
<td>-</td>
</tr>
<tr>
<td>FATAL**</td>
<td>10 (0.06)</td>
<td>37 (0.24)</td>
<td>0.27 (0.13, 0.53)</td>
<td>-</td>
</tr>
<tr>
<td>Intracranial**</td>
<td>4 (0.03)</td>
<td>40 (0.20)</td>
<td>0.13 (0.05, 0.37)</td>
<td>-</td>
</tr>
<tr>
<td>Non-intracranial</td>
<td>6 (0.04)</td>
<td>70 (0.55)</td>
<td>0.84 (0.28, 2.15)</td>
<td>-</td>
</tr>
</tbody>
</table>

* Bleeding events within each subtype were counted once per subject, but subjects may have contributed events to multiple endpoints. Bleeding events were counted during treatment or within 2 days of stopping study treatment (on-treatment period).

** Defined as clinically overt bleeding accompanied by one or more of the following: a decrease in hemoglobin of ≥2 g/dL, a transfusion of 2 or more units of packed red blood cells, bleeding at a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal or with fatal outcome.

† Intracranial bleed includes intracerebral, intraventricular, subdural, and subarachnoid hemorrhage. Any type of hemorrhagic stroke was adjudicated and counted as an intracranial major bleed.

§ On-treatment analysis based on the safety population, compared to ITT analysis presented in Section 14.

Gl bleed includes upper GI, lower GI, and rectal bleeding.

** Fatal bleeding is an adjudicated death with the primary cause of death as intracranial bleeding or non-intracranial bleeding during the on-treatment period.

ARISTOTLE, the results for major bleeding were generally consistent across most major subgroups including age, weight, CHADS2, score (a scale from 0 to 6 used to estimate risk of stroke, with higher scores predicting greater risk), prior warfarin use, geographic region, and aspirin use at randomization (Figure 1). Subjects treated with apixaban with diabetes bled more (3.0% per year) than did subjects without diabetes (1.5% per year).
Table 4:  Adverse Reactions Occurring in ≥1% of Patients in Either Group Undergoing Hip or Knee Replacement Surgery

<table>
<thead>
<tr>
<th></th>
<th>ELIQUIS (apixaban) n (%)</th>
<th>ENOXAPARIN n (%)</th>
<th>Placebo n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>2 (0.2)</td>
<td>1 (0.1)</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>CRINM*</td>
<td>25 (3.3)</td>
<td>34 (4.3)</td>
<td>19 (2.3)</td>
</tr>
<tr>
<td>Major + CRINM</td>
<td>27 (3.2)</td>
<td>35 (4.4)</td>
<td>22 (2.7)</td>
</tr>
<tr>
<td>Minor</td>
<td>75 (9.5)</td>
<td>96 (12.1)</td>
<td>58 (7.5)</td>
</tr>
<tr>
<td>All</td>
<td>94 (11.2)</td>
<td>121 (14.8)</td>
<td>74 (9.8)</td>
</tr>
</tbody>
</table>

Table 7:  Bleeding Results in the AMPLIFY EXT Study

<table>
<thead>
<tr>
<th></th>
<th>ELIQUIS (apixaban) 2.5 mg bid n (%)</th>
<th>ELIQUIS (apixaban) 5 mg bid n (%)</th>
<th>Placebo n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>2 (0.2)</td>
<td>1 (0.1)</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>CRINM*</td>
<td>25 (3.3)</td>
<td>34 (4.3)</td>
<td>19 (2.3)</td>
</tr>
<tr>
<td>Major + CRINM</td>
<td>27 (3.2)</td>
<td>35 (4.4)</td>
<td>22 (2.7)</td>
</tr>
<tr>
<td>Minor</td>
<td>75 (9.5)</td>
<td>96 (12.1)</td>
<td>58 (7.5)</td>
</tr>
<tr>
<td>All</td>
<td>94 (11.2)</td>
<td>121 (14.8)</td>
<td>74 (9.8)</td>
</tr>
</tbody>
</table>

Other Adverse Reactions

Less common adverse reactions in ELIQUIS-treated patients in the AMPLIFY or AMPLIFY-EXT studies occurring at a frequency of ≥0.1% to <1%

<table>
<thead>
<tr>
<th></th>
<th>ELIQUIS n=840</th>
<th>ENOXAPARIN n=840</th>
<th>Placebo n=840</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>2 (0.2)</td>
<td>1 (0.1)</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>CRINM*</td>
<td>25 (3.3)</td>
<td>34 (4.3)</td>
<td>19 (2.3)</td>
</tr>
<tr>
<td>Major + CRINM</td>
<td>27 (3.2)</td>
<td>35 (4.4)</td>
<td>22 (2.7)</td>
</tr>
<tr>
<td>Minor</td>
<td>75 (9.5)</td>
<td>96 (12.1)</td>
<td>58 (7.5)</td>
</tr>
<tr>
<td>All</td>
<td>94 (11.2)</td>
<td>121 (14.8)</td>
<td>74 (9.8)</td>
</tr>
</tbody>
</table>

Adverse reactions occurring in ≥1% of patients in the AMPLIFY or AMPLIFY-EXT studies are listed in Table 8.

Table 8:  Adverse Reactions Occurring in ≥1% of Patients Undergoing Extended Treatment for DVT and PE in the AMPLIFY EXT Study

<table>
<thead>
<tr>
<th></th>
<th>ELIQUIS n=840</th>
<th>ENOXAPARIN n=840</th>
<th>Placebo n=826</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>2 (0.2)</td>
<td>1 (0.1)</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>CRINM*</td>
<td>25 (3.3)</td>
<td>34 (4.3)</td>
<td>19 (2.3)</td>
</tr>
<tr>
<td>Major + CRINM</td>
<td>27 (3.2)</td>
<td>35 (4.4)</td>
<td>22 (2.7)</td>
</tr>
<tr>
<td>Minor</td>
<td>75 (9.5)</td>
<td>96 (12.1)</td>
<td>58 (7.5)</td>
</tr>
<tr>
<td>All</td>
<td>94 (11.2)</td>
<td>121 (14.8)</td>
<td>74 (9.8)</td>
</tr>
</tbody>
</table>

Treatment of pregnant rats from implantation (Day 7) to weaning (Day 21) with apixaban at a dose of 1000 mg/kg (about 5 times the human exposure based on urine clearance) did not result in death of offspring or death of mother rats during lactation in association with uterine bleeding. However, increased incidence of maternal bleeding, primarily during gestation, occurred at apixaban doses ≥0.25 mg/kg, a dose corresponding to ≥1.3 times the human exposure.

Table 9:  Intraoperative Administration

<table>
<thead>
<tr>
<th></th>
<th>ELIQUIS n=266</th>
<th>ENOXAPARIN n=266</th>
<th>Placebo n=266</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>CRINM*</td>
<td>17 (6.4)</td>
<td>12 (4.5)</td>
<td>9 (3.4)</td>
</tr>
<tr>
<td>Major + CRINM</td>
<td>21 (7.9)</td>
<td>18 (6.8)</td>
<td>13 (4.9)</td>
</tr>
<tr>
<td>Minor</td>
<td>57 (21.7)</td>
<td>50 (18.9)</td>
<td>42 (16.1)</td>
</tr>
<tr>
<td>All</td>
<td>74 (28.1)</td>
<td>67 (25.4)</td>
<td>57 (21.7)</td>
</tr>
</tbody>
</table>

* CRINM = clinically relevant nonmajor bleeding

Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Correlation of antepartum, postpartum, and neonatal reactions to apixaban, but was not associated with increased risk for fetal malformations during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Women should be instructed either to discontinue breastfeeding or to discontinue ELIQUIS (apixaban) therapy, taking into account the importance of the drug to the mother.

Pregnancy

No dose adjustment is required in patients with mild hepatic impairment (Child-Pugh class A). Because patients with moderate hepatic impairment (Child-Pugh class B) may have intrinsic coagulation abnormalities and there is limited clinical experience with ELIQUIS in these patients, during recommendations cannot be provided (See Clinical Pharmacology (12.2) in Full Prescribing Information). ELIQUIS is not recommended in patients with severe hepatic impairment (Child Pugh class C). [See Clinical Pharmacology (12.2) in Full Prescribing Information].

OVERDOSAGE

There is no antidote to ELIQUIS. Overdose of ELIQUIS increases the risk of bleeding (see Warnings and Precautions).

In controlled clinical trials, orally administered apixaban in healthy subjects at doses up to 50 mg daily for 1 to 7 days (25 mg daily for 7 days or 50 mg once daily for 3 days) had no clinically significant adverse effects.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Advis patients of the following:

• They should not discontinue ELIQUIS without talking to their physician first.

• They should be informed that it might take longer than usual for bleeding to stop, and they may bruise or bleed more easily when treated with ELIQUIS. Advise patients about how to recognize bleeding problems, including hypotension and the urgent need to report any unusual bleeding to their physician.

• They should tell their physicians and dentists they are taking ELIQUIS, and/or any other medications that may affect bleeding, including nonprescription products, such as aspirin or NSAIDs, before any surgical or medical or dental procedure is scheduled and before any new drug is taken.

• If the patient is having neuromuscular or spinal surgery, inform the patient to watch for signs and symptoms of spinal or epidural hematomas, such as numbness or weakness of the legs, or bowel or bladder dysfunction. [see Warnings and Precautions]. If any of these symptoms occur, the patient should contact their physician immediately.

• They should tell their physicians if they are pregnant or plan to become pregnant or are breastfeeding or intend to breastfeed during treatment with ELIQUIS [see Use in Specific Populations].

If a dose is missed, the dose should be taken as soon as possible on the same day and [see Use in Specific Populations].

Marketed by: Bristol-Myers Squibb Company

Princeton, New Jersey 08540 USA

Pfizer Inc.

New York, New York 10017 USA
Infectious disease hospitalizations on the decline

By Tara Haelle
Frontline Medical News

The rate of pediatric hospitalizations for infectious diseases has decreased overall among U.S. children from 2000 to 2012, though skin infection hospitalizations have climbed, a recent study found.

“The observed reduction in infectious disease hospitalizations (vaccine-preventable diseases and others) supports a cautious optimism that the infectious disease-related morbidity can be further reduced,” Dr. Tadahiro Goto of the department of emergency medicine at Massachusetts General Hospital, Boston, and coauthors reported online.

In their cross-sectional analysis, the authors identified more than 2.2 million pediatric infectious disease hospitalizations, which translated to a weighted estimate of nearly 3.7 million across the five datasets. These hospitalizations comprised almost a quarter (24.5%) of all pediatric hospitalizations over those 12 years, but their rate dropped 16.5%, from 91/10,000 children in 2000 to 75.8/10,000 children in 2012 (P less than .001). A 30.3% decrease in hospitalizations among infants less than 1 year old primarily drove the overall rate decline, alongside a slighter (13.4%) drop in children aged 1-4 years.

Lower respiratory infections, including pneumonia and bronchiolitis, were the most common infectious diseases leading to pediatric hospitalization. Although these accounted for 42.8% of all infectious disease hospitalizations in 2012, their hospitalization rate had dropped 19.1% since 2000, from 40.1 children to 32.5 children per 10,000, driven mostly by a 25.5% drop in pneumonia hospitalizations.

Abdominal and rectal infections comprised 13.8% of all infectious disease hospitalizations in 2012 but had declined 6.9% since 2000. Upper respiratory infections had been the third most common subgroup in 2000 but was replaced by skin infections in 2012.

Hospitalization rates decreased for all infectious disease subgroups except skin infections, perinatal infections, septicemia, and postoperative infections. Skin infections had the biggest jump, 67.6% over the period studied (P less than .001), followed by a 16.7% increase in perinatal infections and smaller increases in the other two subgroups.

The biggest subgroup declines were HIV/AIDS, with an 81.5% drop, and nonviral meningitis, with a 64.9% drop. Mortality in the hospital also declined among children admitted for infectious disease: those admitted in 2012 had 37% reduced odds of death, compared with those admitted in 2000.

The median length of a hospital stay, 2 days, did not change across time, and the median cost for each hospitalization increased 9.6%, from $3,452 in 2003 to $3,784 in 2012. Nationwide, however, infectious disease hospitalizations cost $4.4 billion in 2012.

The research was funded by the National Institutes of Health. Information on disclosures was not provided.
Readmissions drop with asthma meds at discharge

BY AMY KARON
Frontline Medical News

A bedside medication delivery service increased the percentage of asthma patients discharged with medications in hand from 0% to 75%, which helped prevent emergency department readmissions within the next month, according to an exploratory, retrospective analysis.

To our knowledge this report is the first to detail specific strategies to reliably discharge patients with meds in hand,” said Dr. Jonathan Hatoun of Boston University Medical Center and his associates.

Before the intervention, the hospital previously had routinely discharged asthma patients without medications in hand, and in 2011, a survey showed that 37% never filled their prescriptions. Concerned that patients were “unnecessarily suffering,” Dr. Hatoun and his associates assembled a multidisciplinary team that worked for 2 years to improve this outcome measure. They initially asked residents to write prescriptions at least a day before discharge, but they were concerned that treatment plans could change. Next, they asked families to pick up medications at the hospital pharmacy, but parents were reluctant to leave their sick child’s bedside. Therefore, the researchers designed an in-room service in which pharmacists delivered the medications to the child’s room when a parent was present (Pediatrics 2016 Feb 24. doi: 10.1542/peds.2015-0461).

“Copayments were collected in the room, either in cash or with a mobile credit payment system purchased by the pharmacy,” the researchers explained. “Unlike traditional pharmacy pickup, the delivery service allows the patient, parent, nurse, and pharmacist to be together in the patient’s hospital room for teaching with the actual medications available for demonstration.”

The delivery service not only met the project goal to increase the “meds in hand” rate from 0% to 75%, but an analysis of patients with complete insurance claims showed that patients discharged with medications in hand were significantly less likely to return to the emergency department within 30 days of discharge, for any reason, compared with patients who received usual care (odds ratio, 0.22; 95% confidence interval, 0.05-0.99).

“More evidence on the impact of being discharged in possession of discharge medications is needed …,” the investigators noted. “Additional areas of exploration could include how the Meds-in-Hand service affects the patient experience, hospital finances, and clinical outcomes for other medical conditions.”

The authors had no external funding sources or disclosures.

Please contact your Actavis representative for more information

AVYCAZ® and its design are trademarks of Allergan, Inc.

© 2016 Allergan. All rights reserved. AVY41771 01/16
Actavis Pharma, Inc., an Allergan affiliate.
Early peanut consumption protects from allergy

BY BRUCE JANCIN  
Frontline Medical News

LOS ANGELES – A peanut allergy prevention strategy based upon regular consumption of peanut-containing foods from infancy to age 5 continued to provide protection even after peanut intake was halted for a full year from age 5 to 6, according to new results from an extension of the landmark LEAP trial, known as LEAP-On, presented at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

The impetus for LEAP-On was the investigators’ concern that a period of peanut avoidance might cause loss of the protective state. But that didn’t occur. “I think there is no doubt that we have prevented peanut allergy so far in these high-risk children. Next, the LEAP-Ad Lib study will tell us whether we’ve prevented it by age 10,” said Dr. Gideon Lack of King’s College London, who headed LEAP-On.

A second major randomized trial known as EAT (Enquiring About Tolerance) presented at the meeting provided further support for early dietary introduction of allergenic foods. EAT differed from LEAP (Learning Early About Peanut Allergy) and LEAP-On in that it ambitiously randomized infants to early introduction or avoidance of not one but six allergenic foods: peanut, cooked egg, cow’s milk, fish, sesame, and wheat. Also, while LEAP and LEAP-On involved roughly 600 infants known to be at very high risk for allergy, EAT was conducted in a general population of 1,303 infants who weren’t at increased risk, all of whom were exclusively breast-fed until the intervention beginning at age 3 months.

The presentation of the LEAP-On and EAT results at the AAAAI annual meeting was a major event marked by the National Institute of Allergy and Infectious Diseases by same-day release of new NIAID-sponsored draft recommendations for the diagnosis and management of food allergies.

In a press conference held at the AAAAI annual meeting to announce the start of a 45-day public comment period for the draft update of the 2010 guidelines, Dr. Daniel Rotrosen, director of NIAID’s division of allergy, immunology and transplantation, said the new guidelines were developed largely in response to the compelling LEAP findings. That trial demonstrated that sustained consumption of peanut starting in infancy resulted in an 81% lower rate of peanut allergy at age 5 years compared to a strategy of peanut avoidance (N Engl J Med. 2015;372:803-13).

The draft guidelines, now available
INDICATION
Orenitram is a prostacyclin vasodilator indicated for treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity.

The study that established effectiveness included predominately patients with WHO functional class II-III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue disease (19%). When used as the sole vasodilator, the effect of Orenitram on exercise is about 10% of the deficit, and the effect, if any, on a background of another vasodilator is probably less than this.

IMPORTANT SAFETY INFORMATION FOR ORENITRAM
CONTRAINDICATIONS
- Orenitram is contraindicated in patients with severe hepatic impairment (Child Pugh Class C)

WARNINGS AND PRECAUTIONS
- Abrupt discontinuation or sudden large reductions in dosage of Orenitram may result in worsening of PAH symptoms
- Orenitram inhibits platelet aggregation and increases the risk of bleeding
- The Orenitram tablet shell does not dissolve. In patients with diverticulosis, Orenitram tablets can lodge in a diverticulum

Please see the Brief Summary of the Full Prescribing Information for Orenitram on the following page.

For additional information about Orenitram, visit www.orenitram.com or call 1-877-UNITHER (1-877-864-8437).

REFERENCES

Orenitram treprostinil EXTENDED-RELEASE TABLETS dosing that adapts.
Continued from previous page

mend that infants at high risk for peanut allergy because they have severe eczema and/or egg allergy should have introduction of pea-nut-containing food at 4-6 months of age to reduce their risk of peanut allergy, preceded by evaluation us-
5 measures predict 30-day postop rehospitalization

BY MITCHEL L. ZOLER
Frontline Medical News

PHOENIX – A simple, five-element formula can help identify the patients undergoing heart surgery who face the greatest risk for a hospital readmission within 30 days following discharge from their index hospitalization.

The surgeons who developed this formula hope to use it in an investigational program that will target intensified management resources in post-surgical patients who face the highest readmission risk, to cut rehospitalizations and better improve their clinical status and quality of life.

The analysis that produced this formula also documented that the worst offender for triggering rehospitalizations following heart surgery is fluid overload, the proximate readmission cause for 23% of post-surgical patients, Dr. Arman Kilic said at the annual meeting of the Society of Thoracic Surgeons. The next most common cause was infection, which led to 20% of readmissions, followed by arrhythmias, responsible for 8% of readmissions, said Dr. Kilic, a thoracic surgeon at the University of Pennsylvania in Philadelphia.

Because fluid overload, often in the form of pleural effusion, is such an important driver of rehospitalizations, a more targeted management program would include better titration of diuretic treatment to patients following heart surgery, thoracentesis, and closer monitoring of clinical features that flag fluid overload such as weight.

An investigational program to target rehospitalization risk in heart surgery patients is planned at Johns Hopkins Hospital in Baltimore, where Dr. Kilic worked when he performed this analysis. Surgeons at Johns Hopkins are now in the process of getting funding for this pilot program, said Dr. John V. Conte Jr., professor of surgery and director of mechanical circulatory support at Johns Hopkins and a collaborator with Dr. Kilic on developing the risk formula.

“We’ll tailor postoperative follow-up. We’ll get high-risk patients back to the clinic sooner, and we’ll send nurse practitioners to see them to make sure they’re taking their medications and are getting weighed daily,” Dr. Conte said in an interview. “When a patient has heart surgery, they typically retain about 5-10 pounds of fluid. Patients with good renal function give up that fluid easily, but others are difficult to diurese. Many patients go home before they have been fully diuresed, and we need to follow these patients and transition them better to out-of-hospital care.”

He noted that other situations also come up that unnecessarily drive patients back to the hospital when an alternative and less expensive intervention might be equally effective. For example, some patients return to the hospital out of concern for how their chest wound is healing. Instead of being rehospitalized, such patients could be reassured by having them send a nurse a photo of their wound or by coming to an outpatient clinic.

Developing improved ways to manage recent heart surgery patients following discharge becomes even more critical later this year when, in July, the Centers for Medicare & Medicaid Services adds 30-day readmissions following coronary artery bypass grafting (CABG) to its list of procedures that can generate a penalty to hospitals if they exceed U.S. norms for readmission rates.

The risk model developed by Dr. Kilic, Dr. Conte, and their associates used data collected from 5,360 heart surgery patients treated at Johns Hopkins during 2008-2013. Nearly half the patients underwent isolated CABG, and 20% had isolated valve surgery. Overall, 585 patients (11%) had a hospital readmission within 30 days of their index discharge. One limitation of the analysis was it used data only on readmissions back to Johns Hopkins Hospital.

The researchers used data from three-quarters of the database to derive the risk formula, and from the remaining 25% of the database to validate the formula. A multivariate analysis of demographic and clinical characteristics that significantly linked with an elevated risk for readmissions identified five factors that independently made a significant contribution to readmission risk, assigning each factor points, depending on its relative contribution to readmission risk in the adjusted model: Severe chronic lung disease received 6 points; placement of a ventricular assist device received 5 points, while other types of heart surgery that was not CABG or valve surgery received 4 points (isolated CABG, isolated valve, or combined CABG and valve surgery received 0 points); development of acute renal failure postoperatively but before index discharge received 4 points; an index length of stay beyond 7 days received 4 points; and African American race received 3 points. The maximum number of points a patient could receive was 22.

Patients with a score of 0 had a 6% rate of a 30-day readmission; those with a score of 22 had a 63% readmission rate. The researchers found a 96% correlation when comparing these predicted readmission risk rates based on the derivation-subgroup analysis with the actual readmission rates seen in the validation subgroup of their database. The targeted risk-management program planned by Dr. Conte would primarily focus on high-risk patients. Dr. Kilic and Dr. Conte said they had no relevant financial disclosures.

mzoler@frontlinemedcom.com
On Twitter @mitchelzoler

VIEW ON THE NEWS

Dr. Francis J. Podbielski, FCCP, comments: Dr. Kilic’s data illustrates common factors resulting in rehospitalization after cardiac surgery. Fastidious fluid management in these patients and others is critical to reduce hospital readmissions. A further point to consider is that many pleural effusions, especially those on the left side, are due to retained hemothorax rather than fluid overload. In those instances, early surgical intervention with video-assisted thorascopic surgery, rather than prolonged diuresis, would be optimal.

Cadaveric allograft sternal replacement appears safe

BY DOUG BRUNK
Frontline Medical News

PHOENIX – Cadaveric allograft sternal replacement has proven to be safe, providing optimal stability to the chest wall and protection of surrounding organs, an analysis of 18 cases demonstrated.

“The allograft was biologically well tolerated, allowing a perfect integration into the host,” Dr. Giuseppe Marulli said at the annual meeting of the Society of Thoracic Surgeons. “Donor cryopreserved sternochordal allograft may become the ideal way for anterior chest wall reconstruction, particularly for wide resections.”

Dr. Marulli, a thoracic surgeon at the University of Padova, Italy, noted that prior experimental studies have demonstrated that cryopreserved bone allografts preserve osteoconduction and osteoinduction capacity (Eur Spine J. 2001 Oct;10:S96-101). “Therefore, they form the basis for new bone tissue formation, allowing for the capillary and perivascular blood supply,” he said.

Limitations of current materials used for sternal reconstruction include “excessive rigidity with risk of erosion and insufficient support for large chest wall defects,” he said. Perceived advantages of using cadaveric bone allograft include easy incorporation, no risk of rejection, and a low risk of infection. For each procedure used in the current analysis, cadaveric allograft sternums with costal cartilages were harvested with an aseptic method and treated with an antibiotic solution for 72 hours. Next, they were cryopreserved at –80ºC and underwent microbiologic testing for at least 1 month to ensure sterility and absence of immunogenic capacity.

Continued on page 45
INDICATION AND USAGE
DALIRESP® (roflumilast) is indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. DALIRESP® is not a bronchodilator and is not indicated for the relief of acute bronchospasm.

IMPORTANT SAFETY INFORMATION
Contraindications
DALIRESP® (roflumilast) is contraindicated in patients with moderate to severe liver impairment (Child-Pugh B or C).

Warnings and Precautions
• DALIRESP® is not a bronchodilator and should not be used for the relief of acute bronchospasm
• Prescribers should advise patients, their caregivers, and families to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if such changes occur, to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment if such events occur. Before using DALIRESP® in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with DALIRESP®.
• Treatment with DALIRESP® is associated with an increase in psychiatric adverse reactions. In controlled clinical trials 5.9% of patients treated with DALIRESP® reported psychiatric adverse reactions vs 3.3% treated with placebo. The most common psychiatric adverse reactions were insomnia (2.4% vs 1.0%), anxiety (1.4% vs 0.9%), and depression (1.2% vs 0.9%). Three patients treated with DALIRESP® experienced suicide-related adverse reactions (one completed suicide and two suicide attempts) compared to one patient (suicidal ideation) treated with placebo.
• Patients should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated and treatment discontinuation considered.
• In addition to weight loss being reported as a common adverse reaction (7.5% of patients treated with DALIRESP® vs 2.1% placebo), weight was prospectively assessed in two 1-year clinical trials. In these studies that compared DALIRESP® to placebo, 20% vs 7% experienced moderate...
The first and only once-daily tablet to provide enhanced protection against COPD exacerbations\(^2\)

- **DALIRESP** is not a bronchodilator and should not be used for the relief of acute bronchospasm

In the two 1-year pivotal studies:

- **Significantly reduced the rate of moderate or severe exacerbations**\(^1\) on top of current bronchodilator therapy\(^2\)

---

**REDUCTION IN THE RATE OF EXACERBATIONS VERSUS PLACEBO\(^3\)**

<table>
<thead>
<tr>
<th></th>
<th>Mean rate of exacerbations (per patient per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo + Bronchodilators</strong> (n=1554)</td>
<td>1.37</td>
</tr>
<tr>
<td><strong>DALIRESP + Bronchodilators</strong> (n=1537)</td>
<td>1.14</td>
</tr>
</tbody>
</table>

\(P=0.0003\) vs placebo

99%–100% were also concurrently taking SABA\(^1\)

---

weight loss (5–10% of body weight) and 7% vs 2% experienced severe weight loss (>10% body weight). During the follow-up period after discontinuing DALIRESP, the majority of patients regained some of the weight they had lost.

- **Use with strong cytochrome P450 enzyme inducers (eg, rifampin, phenobarbital, carbamazepine, phenytoin)** is not recommended, as they decrease the exposure and may reduce the therapeutic effectiveness of DALIRESP.

**Adverse Reactions**

In clinical trials, the most common adverse reactions (>2% and greater than placebo) were diarrhea (9.5% vs 2.7%), weight loss (7.5% vs 2.1%), nausea (4.7% vs 1.4%), headache (4.4% vs 2.1%), back pain (3.2% vs 2.2%), influenza (2.8% vs 2.7%), insomnia (2.4% vs 1.0%), dizziness (2.1% vs 1.1%), and decreased appetite (2.1% vs 0.4%).

**Please see Brief Summary on the following page.**

---

\(^1\) Patients were allowed to be on LABA or SAMA at stable doses. SABA was allowed for rescue use. In the pooled analysis, the use of concomitant bronchodilators in the placebo group vs DALIRESP group were: LABA (91% vs 49%), SAMA (37% vs 35%), and SABA (99% vs 100%).

**Study design:** A pooled analysis of two identical, 1-year, double-blind, placebo-controlled studies of 3091 patients with severe COPD associated with chronic bronchitis and a history of exacerbations compared DALIRESP (n=1537) and placebo (n=1554). Subjects were current or ex-smokers with a smoking history of \(>20\) pack-years, aged \(>40\) with a clinical diagnosis of COPD with chronic cough and sputum production. The study included a 4-week run-in period followed by a 1-year treatment period. Subjects could use SABAs as needed and could continue treatment with LABAs or SAMAs at stable doses. The studies were designed to assess the rate of moderate or severe COPD exacerbations and the change from baseline in pre-bronchodilator FEV\(_1\).

DALIRESP® (roflumilast) tablets

INDICATIONS AND USAGE
DALIRESP® is indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.

Contraindications
The use of DALIRESP is contraindicated in the following conditions:

- Moderate to severe liver impairment (Child-Pugh B or C) [see Clinical Pharmacology (12.3) and Use in Specific Populations (8.6) in the full Prescribing Information].

- Known hypersensitivity to roflumilast.

DOSE AND ADMINISTRATION
The recommended dose of DALIRESP is one 500 microgram (mcg) tablet per day, with or without food.

CONTRAINDICATIONS
The use of DALIRESP is contraindicated in the following conditions:

- Moderate to severe liver impairment (Child-Pugh B or C) [see Clinical Pharmacology (12.3) and Use in Specific Populations (8.6) in the full Prescribing Information].

- Known hypersensitivity to roflumilast.

ADVERSE REACTIONS
The most common adverse reactions in the DALIRESP group included stomach pain, diarrhea, and nausea.

Table 1: Adverse Reactions Reported by ≥2% of Patients Treated with DALIRESP 500 mcg daily and Greater Than Placebo

<table>
<thead>
<tr>
<th>Adverse Reactions (Preferred Term)</th>
<th>DALIRESP</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>240 (9.5)</td>
<td>113 (2.7)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>331 (7.5)</td>
<td>89 (2.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>209 (4.7)</td>
<td>60 (1.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>199 (4.4)</td>
<td>67 (2.1)</td>
</tr>
<tr>
<td>Back pain</td>
<td>142 (3.2)</td>
<td>92 (2.4)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>124 (2.6)</td>
<td>112 (2.7)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>105 (2.4)</td>
<td>41 (1.0)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>91 (2.1)</td>
<td>55 (1.4)</td>
</tr>
</tbody>
</table>

Postmarketing Experience
The following adverse reactions have been identified from spontaneous reports of DALIRESP received worldwide and have not been listed elsewhere. These adverse reactions have been chosen for inclusion due to a combination of seriousness, frequency of reporting or potential causal connection to DALIRESP. Because these adverse reactions were reported voluntarily from a population of uncertain size, it is not possible to estimate their frequency or establish a causal relationship to DALIRESP exposure.

DRUG INTERACTIONS
A major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP3A4 and CYP1A2 (see Clinical Pharmacology (12.3) in the full Prescribing Information). Daliresp® (roflumilast) induces systemic exposure to roflumilast and may reduce the therapeutic effectiveness of DALIRESP. Therefore the use of strong cytochrome P450 inducers (e.g., rifampicin, phenobarbital, carbamazepine, and phenytoin) with DALIRESP is not recommended [see Drug Interactions (5.4) and Clinical Pharmacology (12.3) in the full Prescribing Information].

Oral Contraceptives Containing Gestodene and Ethinyl Estradiol
The co-administration of DALIRESP (500 mcg) with oral contraceptives containing gestodene and ethinyl estradiol may increase roflumilast systemic exposure and may result in increased side effects. The risk of such concurrent use should be weighed carefully against benefit [see Clinical Pharmacology (12.3) in the full Prescribing Information].

USE IN SPECIFIC POPULATIONS
Pregnancy
Teratogenic effects: Pregnancy Category C. There are no adequate and well-controlled studies of DALIRESP in pregnant women. DALIRESP should not be used during pregnancy even if the potential benefit justifies the potential risk to the fetus. DALIRESP induced stillbirth and decreased pup viability in mice at doses corresponding to approximatively 16 and 40 times, respectively, the maximum recommended human dose (MRHD) on a mg/m² basis at maternal doses >2 mg/kg/day and 6 mg/kg/day, respectively. DALIRESP induced post-implantation loss in rats at doses greater than or equal to approximately 10 times the MRHD (on a mg/kg basis at maternal doses >2.5 mg/kg/day). No treatment-related effects on embryo-fetal development were observed in mice, rats, and rabbits at approximately 12.3 and 25 times the MRHD, respectively (on a mg/m² basis at maternal doses of 1.5, 12, and 0.8 mg/kg/day, respectively).

Nursing Mothers
Roflumilast and/or its metabolites are excreted into the milk of lactating rats. Excretion of roflumilast and/or its metabolites into human milk is probable. There are no human studies that have investigated effects of DALIRESP on nursing infants. DALIRESP should not be used by women who are nursing.

Pediatric Use
DALIRESP does not normally occur in children. The safety and effectiveness of DALIRESP in pediatric patients have not been established.

Geriatric Use
Of the 4384 COPD subjects exposed to DALIRESP for up to 12 months in 8 controlled clinical trials, 2022 (46%) years of age and 471 were ≥75 years of age. 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 in the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Based on available data for roflumilast, no adjustment of dosage in geriatric patients is warranted [see Clinical Pharmacology (12.3) in the full Prescribing Information].

Hepatic Impairment
Roflumilast 250 mg once daily for 14 days was studied in subjects with mild-to-moderate hepatic impairment classified as Child-Pugh-B and C subjects in each group. The AUCs of roflumilast and roflumilast N-oxide were increased by 51% and 24%, respectively, in Child-Pugh-B subjects and by 82% and 41%, respectively, in Child-Pugh-C subjects, as compared to age-, weight- and gender-matched healthy subjects. The Cmax of roflumilast and roflumilast N-oxide were increased by 3% and 26%, respectively, in Child-Pugh-A subjects and by 12% and 40%, respectively, in Child-Pugh-B subjects, as compared to healthy subjects. DALIRESP has not been studied in hepatologically impaired patients. Clinicians should consider the risk-benefit of administering DALIRESP to patients who have mild liver impairment (Child-Pugh A). DALIRESP is not recommended for use in patients with moderate or severe liver impairment (Child-Pugh B or C) [see Contraindications (4) and Clinical Pharmacology (12.3) in the full Prescribing Information].

Renal Impairment
In twelve subjects with severe renal impairment administered a single dose of 500 mg roflumilast, the AUCs of roflumilast and roflumilast N-oxide were decreased by 27% and 7%, respectively and Cmax were reduced by 16% and 12%, respectively. No dosage adjustment is necessary for patients with renal impairment [see Clinical Pharmacology (12.3) in the full Prescribing Information].

OVERDOSAGE
Human Experience
No case of overdose has been reported in clinical studies with DALIRESP. During the Phase I studies of DALIRESP, the following symptoms were observed at an increased rate after a single oral dose of 2500 mg and a single dose of 5000 mg: headache, gastrointestinal disturbances, dizziness, palpitations, lightheadedness, clamminess and arterial hypotension.

Management of Overdose
In case of overdose, patients should seek immediate medical help. Appropriate supportive medical care should be provided. Since roflumilast is highly protein bound, hemodialysis is not likely to be an efficient method of drug removal. It is not known whether roflumilast is dialyzable by peritoneal dialysis.

PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Distributed by:
AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

DALIRESP® is a registered trademark of Takeda GmbH.

© AstraZeneca 2015

3217200 1/16

bs.11/15
Complications after cancer surgery raise death risk

BY NEIL OSTERWEIL
Frontline Medical News

BOSTON – The operation was a success, but the patient died.

It’s an old chestnut for sure, but there is a painful kernel of truth in it, say investigators who found that patients who undergo complex cancer surgery and have serious complications are at significantly increased risk for death for at least 6 months after surgery, compared with patients who undergo the same procedure with few or no complications.

“Our work has important implications for quality assessment. I think in cancer surgery in particular we have to get away from the short-term metrics of survival, and we have to think about the implications of complications for long-term survival, even if at a very high-quality hospital we’re good at salvaging those patients who do experience those complications,” said Dr. Hari Nathan of the University of Michigan, Ann Arbor.

In a retrospective study, results of which were presented at the annual Society of Surgical Oncology Cancer Symposium, Dr. Nathan and colleagues showed that patients who underwent surgery for cancers of the esophagus and lung who had serious complications but survived at least 30 days after surgery had a more than twofold greater risk for death than did patients who had no complications, and patients with serious complications following surgery for cancer of the pancreas had a nearly twofold greater risk.

The effects of serious complications on survival persisted out to at least 180 days after surgery for each of the three procedures.

The findings suggest that just getting the patient through the operation and keeping him or her alive in the ICU is not sufficient cause for celebration by surgeons, Dr. Nathan said.

The investigators conducted the study to examine the incidence of complications following cancer surgery in older patients, the relationship between surgical complications and long-term survival, and whether

### Hazard ratios for death after surgery with serious complications

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Hazard Ratio (HR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophageal cancer</td>
<td>2.0</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>1.5</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Note: Based on Surveillance, Epidemiology and End Results-Medicare data for patients who underwent surgery for esophageal cancer (n = 965), non–small cell lung cancer (n = 12,395), and pancreatic adenocarcinoma (n = 1,966).

Source: Dr. Nathan

Looking only at those patients with lung cancer who survived at least 30 days after surgery, the investigators found that median survival among those who had no complications was 79 months, compared with 60 months for those who had mild complications, and 33 months for patients who had serious complications (P less than .001)

“And indeed, when we performed adjusted survival analyses looking at all three disease sites, we saw a very consistent story: that those patients who had serious complications had decreased long-term survival for all three malignancies we looked at,” Dr. Nathan said.

Specifically, in survival analyses adjusted for sex, age, and procedure code, hazard ratios for patients with serious complications compared with those who had no complications were 2.35 for esophageal cancer patients, 2.13 for lung cancer patients, and 1.57 for pancreatic cancer patients (all comparisons significant as shown by 95% confidence intervals).

The investigators questioned whether the differences in mortality were due to the late effects of perioperative complications.

“In modern ICUs, we can keep virtually anybody alive for 30 days, and there has been a lot interest in longer-term metrics for perioperative mortality, for example, at 30 or 90 days, so we thought maybe that’s what we were seeing here,” he said.

To test this idea, the investigators looked at the effects of complications on patient who survived lung cancer surgery for at least 90 days, and those who lived for at least 180 days after surgery, and they saw that the survival curves were similar to those seen with the 30-day survivors, showing significantly and persistently worse survival for patients with serious complications (P less than .001).

For each of the disease states, patients with serious complications were also significantly less likely than those with no or mild complications to receive adjuvant chemotherapy, even after adjustment for patient age and cancer stage, two significant determinants of the likelihood of receiving chemotherapy.

And even when the effect of chemotherapy for those who did receive it was added into the survival models, patients with serious complications still had significantly worse overall survival, Dr. Nathan noted.

“Serious complications after these three cancer resections are common and they are associated with dramatically inferior long-term survival,” he said.

The study was internally funded. Dr. Nathan reported no significant disclosures.

Continued from page 41

Dr. Marulli reported results from 18 patients who underwent the procedure between January 2009 and January 2015, 13 of whom were female. Their median age was 59 years, their median tumor diameter was 4.75 cm, most (88%) had undergone preoperative needle biopsy, and 50% had undergone induction therapy.

The main indication for sternectomy was a single-site sternal metastasis (nine patients), primary chondrosarcoma (four cases), sternal dehiscence after cardiac surgery (two cases), malignant fibrous tumor (one case), radiioduced soft-tissue sarcoma (one case), and a thymic carcinoma invading the sternum (one case).

All patients were extubated in the OR, and one patient died in the hospital from a pulmonary embolism. Two patients (11%) developed postoperative complications: one case of Candida urinary infection and one case of bleeding at the site of the muscle flap. The median postoperative length of stay was 11 days.

To date, no infections or rejections of the grafts have occurred.

Dr. Marulli said. After a median of 36 months, 13 patients are alive and 4 are dead (3 from a metastatic recurrence and 1 from an unrelated cause). One patient required removal of a clavicular screw for dislocation 4 months after the operation.

“The outcomes [of these procedures] appear to be excellent,” said Dr. Francis J. Podbielski, FCCP.

Dr. Marulli reported having no financial disclosures.

dbrunk@frontlinemedcom.com
Top 5 EHR companies agree to halt data blocking

BY CHERYL CLARK
Frontline Medical News

LAS VEGAS – Health care data interoperability should get a huge boost under a public-private effort announced Feb. 29 by U.S. Department of Health and Human Services Secretary Sylvia Burwell.

The nation’s top five health care systems and companies, which provide the electronic health record systems that cover more than 90% of U.S. hospital patients, have agreed to principles designed to improve patient access to health data and eliminate the practice of data blocking.

They also have agreed to adopt federally recognized, national interoperability standards, Ms. Burwell announced at the annual meeting of the Healthcare Information and Management Systems Society.

“Technology is not just one leg of our strategy to build a better health care system for our nation—it supports the entire effort,” Ms. Burwell said. “We are working to unlock health care data and information so that providers are better informed and patients and families can access their health care information, making them empowered, active participants in their own care.”

In a show of support, medical specialty societies including the American Academy of Family Physicians, the American College of Physicians, the American Society of Clinical Oncology and the American Medical Association also signed on to the commitment.

“We have made tremendous progress to bring health care into the 21st century,” Ms. Burwell said. “In 6 short years, we have tripled the adoption of electronic health records. Today, three-quarters of physicians are using them. And nearly every hospital uses EHRs, meaning that there is now a digital care footprint for almost everyone in this country.”

To unlock all those data and make them useful to health care providers and patients, the health IT companies and health care systems have agreed to the following steps:

• Implement application programming interface (API) technology so that smartphone and tablet apps can be created, facilitating patient use and transfer of their health care data.

• Work so providers can share patient health care data with patients and other providers whenever permitted by law, while not blocking such sharing either intentionally or unintentionally.

• Use the federally recognized Fast Healthcare Interoperability Resources (FHIR) data standard.

“This commitment is a ‘major step forward’ to help patients ‘not just in one episode, but over the long term,’ explained Dr. Karen DeSalvo, National Coordinator for Health Information Technology.

The agreement means the health care system is “on the threshold of a truly historic opportunity to transform quality of care,” she added.

Federal officials have a timeline for progress toward these goals by 2018, Dr. DeSalvo noted. But “the private sector wants to pull that forward and be leaders with us,” she said. “So, our expectation is that the calls and the commitments and the associated actions that these developers have declared will be seeing some changes by the fall.”

To highlight health information technology’s promise, Ms. Burwell shared a story about electronic health records’ use to find children affected by lead pollution in the water supplies of Flint, Mich.

Alerted to the problem by a friend, pediatrician Mona Hanna-Attisha of Hurley Medical Center in Flint tried to determine whether pipe corrosion might leach dangerous levels of lead into the water supply, Ms. Burwell said.

“She knew the danger lead posed and began what she called a ‘crusade’ to find out if it was affecting children,” Ms. Burwell explained. Dr. Hanna-Attisha mined Hurley’s medical records to “compare blood test results from more than 700 children in the area and map home addresses for geographic variations.

“She quickly discovered that the percentage of children in Flint with lead poisoning had doubled,
With mild temperatures and sunshine nearly 300 days a year, Los Angeles is often described as “perfect.” And, it’s a perfect setting for CHEST 2016, where we’ll connect a global community in clinical chest medicine. As always, our program will deliver current pulmonary, critical care, and sleep medicine topics presented by world-renowned faculty in a variety of innovative instruction formats.

Watch for Details
chestmeeting.chestnet.org

Connecting a Global Community in Clinical Chest Medicine
OCTOBER 22 - 26

and even tripled, in some neighborhoods,” Burwell said.

If those results had still been on paper, “it would have taken forever to get these results,” she said.

“Dr. Hanna-Attisha’s story shows us the power of putting health care data to work,” Ms. Burwell noted. “It helps us put patients in the center of their care.”

Dr. Mike Nelson, FCCP, comments: If this agreement leads to substantive changes in the current EHR quagmire it will indeed be a huge benefit for physicians and patients alike. There is little more frustrating to both the patient and the physician than having to evaluate an individual whose records are “locked” in another hospital’s system. The adoption of federal standards should result in a significant improvement in the current situation although, as stated in the article, implementation may be slow and difficult. I would offer Ms. Burwell the following suggestion; invent a process called “Meaningful Implementation” and tax EHR vendors 2-8% for each year they do not comply.

HRSA redefines ‘investigation’

BY ALICIA GALLEGOS
Frontline Medical News

AUSTIN, TEX. – Physicians could face more reportable actions to the National Practitioner Data Bank (NPDB) under changes to the data bank’s guidebook.

In its last update of the guidebook, the Health Resources and Services Administration (HRSA) expanded its definition of “investigation” and now interprets the term “expansively” and will not be limited by how hospital bylaws define an investigation.

Data bank officials will review a health care entity’s bylaws and other documents for assistance in determining whether an investigation has started or is ongoing, but they retain “the ultimate authority to determine whether an investigation exists,” according to the guidebook.

The change is significant because it means more reviews by health care entities could be considered investigations by the data bank, regardless of how hospitals regard the assessment, Michael A. Cassidy said at the meeting, which was held by the American Health Lawyers Association.

Investigations alone are not reportable to the data bank, but actions taken by doctors during investigations are. This includes:

- Resignation of clinical privileges.
- Failure to renew clinical privileges.
- Lapse of license.
- Leave of absence.

- Relinquishment of panel membership.

The guidebook notes that a routine, formal peer review process under which a health care entity evaluates, against defined measures, privilege-specific competence of all practitioners is not considered an investigation by the NPDB. However, a formal, “targeted process used when issues related to a specific practitioner’s professional competence or conduct are identified” is considered an investigation for purposes of reporting to the NPDB.

The catch for doctors is that their awareness of an investigation is immaterial, said Mr. Cassidy, a Pittsburgh-based health law attorney. In the past, a doctor’s awareness of an investigation was a prerequisite for filing a report with the data bank.

The HRSA’s stance is that “physicians’ awareness of the investigation doesn’t have any impact on whether it’s an investigation or not,” Mr. Cassidy said in an interview. “From a physician standpoint, they want to be aware all the time whether an investigation has started. If they don’t find out an investigation has started until after they get a decision, it’s too late to forestall any of the reporting consequences.”

In addition, the NPDB considers an investigation ongoing until the health care entity takes a final action or formally closes the investigation. Written notice to the doctor would likely be the best evidence of formal closure, Mr. Cassidy says.

agallegos@frontlinemedcom.com
On Twitter @legal_med

Dr. Mike Nelson, FCCP, comments: If this agreement leads to substantive changes in the current EHR quagmire it will indeed be a huge benefit for physicians and patients alike. There is little more frustrating to both the patient and the physician than having to evaluate an individual whose records are “locked” in another hospital’s system. The adoption of federal standards should result in a significant improvement in the current situation although, as stated in the article, implementation may be slow and difficult. I would offer Ms. Burwell the following suggestion; invent a process called “Meaningful Implementation” and tax EHR vendors 2-8% for each year they do not comply.

HRSA redefines ‘investigation’

BY ALICIA GALLEGOS
Frontline Medical News

AUSTIN, TEX. – Physicians could face more reportable actions to the National Practitioner Data Bank (NPDB) under changes to the data bank’s guidebook.

In its last update of the guidebook, the Health Resources and Services Administration (HRSA) expanded its definition of “investigation” and now interprets the term “expansively” and will not be limited by how hospital bylaws define an investigation.

Data bank officials will review a health care entity’s bylaws and other documents for assistance in determining whether an investigation has started or is ongoing, but they retain “the ultimate authority to determine whether an investigation exists,” according to the guidebook.

The change is significant because it means more reviews by health care entities could be considered investigations by the data bank, regardless of how hospitals regard the assessment, Michael A. Cassidy said at the meeting, which was held by the American Health Lawyers Association.

Investigations alone are not reportable to the data bank, but actions taken by doctors during investigations are. This includes:

- Resignation of clinical privileges.
- Failure to renew clinical privileges.
- Lapse of license.
- Leave of absence.

- Relinquishment of panel membership.

The guidebook notes that a routine, formal peer review process under which a health care entity evaluates, against defined measures, privilege-specific competence of all practitioners is not considered an investigation by the NPDB. However, a formal, “targeted process used when issues related to a specific practitioner’s professional competence or conduct are identified” is considered an investigation for purposes of reporting to the NPDB.

The catch for doctors is that their awareness of an investigation is immaterial, said Mr. Cassidy, a Pittsburgh-based health law attorney. In the past, a doctor’s awareness of an investigation was a prerequisite for filing a report with the data bank.

The HRSA’s stance is that “physicians’ awareness of the investigation doesn’t have any impact on whether it’s an investigation or not,” Mr. Cassidy said in an interview. “From a physician standpoint, they want to be aware all the time whether an investigation has started. If they don’t find out an investigation has started until after they get a decision, it’s too late to forestall any of the reporting consequences.”

In addition, the NPDB considers an investigation ongoing until the health care entity takes a final action or formally closes the investigation. Written notice to the doctor would likely be the best evidence of formal closure, Mr. Cassidy says.

agallegos@frontlinemedcom.com
On Twitter @legal_med

Dr. Mike Nelson, FCCP, comments: If this agreement leads to substantive changes in the current EHR quagmire it will indeed be a huge benefit for physicians and patients alike. There is little more frustrating to both the patient and the physician than having to evaluate an individual whose records are “locked” in another hospital’s system. The adoption of federal standards should result in a significant improvement in the current situation although, as stated in the article, implementation may be slow and difficult. I would offer Ms. Burwell the following suggestion; invent a process called “Meaningful Implementation” and tax EHR vendors 2-8% for each year they do not comply.

HRSA redefines ‘investigation’

BY ALICIA GALLEGOS
Frontline Medical News

AUSTIN, TEX. – Physicians could face more reportable actions to the National Practitioner Data Bank (NPDB) under changes to the data bank’s guidebook.

In its last update of the guidebook, the Health Resources and Services Administration (HRSA) expanded its definition of “investigation” and now interprets the term “expansively” and will not be limited by how hospital bylaws define an investigation.

Data bank officials will review a health care entity’s bylaws and other documents for assistance in determining whether an investigation has started or is ongoing, but they retain “the ultimate authority to determine whether an investigation exists,” according to the guidebook.

The change is significant because it means more reviews by health care entities could be considered investigations by the data bank, regardless of how hospitals regard the assessment, Michael A. Cassidy said at the meeting, which was held by the American Health Lawyers Association.

Investigations alone are not reportable to the data bank, but actions taken by doctors during investigations are. This includes:

- Resignation of clinical privileges.
- Failure to renew clinical privileges.
- Lapse of license.
- Leave of absence.

- Relinquishment of panel membership.

The guidebook notes that a routine, formal peer review process under which a health care entity evaluates, against defined measures, privilege-specific competence of all practitioners is not considered an investigation by the NPDB. However, a formal, “targeted process used when issues related to a specific practitioner’s professional competence or conduct are identified” is considered an investigation for purposes of reporting to the NPDB.

The catch for doctors is that their awareness of an investigation is immaterial, said Mr. Cassidy, a Pittsburgh-based health law attorney. In the past, a doctor’s awareness of an investigation was a prerequisite for filing a report with the data bank.

The HRSA’s stance is that “physicians’ awareness of the investigation doesn’t have any impact on whether it’s an investigation or not,” Mr. Cassidy said in an interview. “From a physician standpoint, they want to be aware all the time whether an investigation has started. If they don’t find out an investigation has started until after they get a decision, it’s too late to forestall any of the reporting consequences.”

In addition, the NPDB considers an investigation ongoing until the health care entity takes a final action or formally closes the investigation. Written notice to the doctor would likely be the best evidence of formal closure, Mr. Cassidy says.

agallegos@frontlinemedcom.com
On Twitter @legal_med

Dr. Mike Nelson, FCCP, comments: If this agreement leads to substantive changes in the current EHR quagmire it will indeed be a huge benefit for physicians and patients alike. There is little more frustrating to both the patient and the physician than having to evaluate an individual whose records are “locked” in another hospital’s system. The adoption of federal standards should result in a significant improvement in the current situation although, as stated in the article, implementation may be slow and difficult. I would offer Ms. Burwell the following suggestion; invent a process called “Meaningful Implementation” and tax EHR vendors 2-8% for each year they do not comply.
We’re gearing up to visit the entertainment capital of the world on October 22-26 for CHEST 2016. We will dazzle Los Angeles and the chest medicine community with current pulmonary, critical care, and sleep medicine topics presented by world-renowned faculty in a variety of innovative instruction formats. You won’t want to miss our cutting-edge education; and, in your free time, we want to make sure you take in all that Los Angeles has to offer. Follow our suggestions below, and we’ll make sure you’ve seen the most famous hot spots in LA.

Hollywood
When you think of Los Angeles, Hollywood is sure to be top of mind. Hollywood is about a 25-minute drive from the Convention Center, so make sure you have time for a longer excursion. You’ll enjoy the recognizable Hollywood sign, built in 1923, and the Hollywood Walk of Fame. You can also check out the Dolby Theater, home to the Academy Awards until at least 2033, or Runyon Canyon, a famous park known for great views of the city and celebrity sightings.

Beaches
If Hollywood doesn’t allure you, maybe you’d rather take it easy at one of Los Angeles’s famous beaches. If you like to people watch, Venice Beach will keep you interested with body builders, jugglers, palm readers, folk artists, and other personalities. If you’re interested in surfing, Malibu Surfrider Beach is where amateurs and experienced surfers alike find great waves. Santa Monica Beach is popular for its volleyball, bike riding, and sunbathing. Or check out Long Beach, home to the Queen Mary, a floating hotel aboard an iconic 1936 ocean liner. With 75 miles of coast, you’re sure to find the beach that you’re looking for.

Shopping
Make sure to explore the LA Fashion District in downtown LA, where you’ll find many top shopping centers to choose from. If you’re looking for luxury, Rodeo Drive in Beverly Hills offers extravagant shopping and dining experiences. Or, if you’re intrigued by bargain hunting, there are also plenty of opportunities for outlet shopping in Camarillo, the Citadel, Desert Hills, and Ontario Mills.

Television Show Taping
Maybe you’ve always dreamed of being part of a live studio audience. Choose from a wide array of shows filmed in Los Angeles, and lucky you, October is in the heart of peak production season. If you want to attend a show taping, order tickets in advance. Check out a vendor, such as Audiences Unlimited or Hollywood Tickets, both of which feature sitcoms and talk shows. You can also look at a specific show’s website to find tickets. Attending a TV show taping can be an exciting and unique LA experience, and, best of all, it’s free!

Los Angeles will keep you entertained with its glamour and glitz. Learn more about tourism opportunities at discoverlosangeles.com, and find out more about CHEST 2016 at chestmeeting.chestnet.org.

CHEST Foundation Grants: How will you champion lung health?

The CHEST Foundation expanded its grant offerings in 2016 with the addition of two new research grants that will broaden the program’s reach and scope. As of February 1, the foundation began accepting applications for research grants, community service projects, and distinguished scholar research projects. These grants have a powerful impact on our grantees’ ability to champion lung health, and they also assist young investigators like Dr. Kerri Johannson in gaining research and project management skills, while assisting in advancing their careers.

“Being awarded a grant is validation that somebody else believes in your idea and that your project could be fruitful and contribute meaningfully to the field,” stated Johannson. “It actually begets more opportunities. I am forever grateful to the CHEST Foundation for providing me with this opportunity.”

The CHEST Foundation’s Clinical Research Grant in Pulmonary Fibrosis, along with Genentech, funded her 2013 project, Ambient Air Pollution Exposure and Clinical Outcomes in Idiopathic Pulmonary Fibrosis. Dr. Johannson’s research focuses on analyzing air pollution exposures and short-term variability in lung function for patients with idiopathic pulmonary fibrosis (IPF).

Her patients were given home breathing machines to monitor how their lung function fluctuated over shorter periods of time. “I was interested in looking at whether or not and how that correlated with their air quality in the regional area.” She said about her project, “No one has ever looked at it before. It’s usually a long-term study, such as every 3 months or changes over a year in clinical trials, but it turns out there is actually a large portion of patients with a lot of short-term variability that has an impact for clinical trial outcomes and measures.”

The deadline for applications is quickly approaching. CHEST Foundation grants help make your research and community service projects possible. Please take advantage of our substantial grant program, and remember that the submissions will be accepted until April 30. How will you help champion lung health? Apply for a CHEST Foundation grant today by going to chestnet.org/grants.

In Memoriam

Dr. Robert O. Crapo, FCCP, died on December 26, 2015. He was a Professor of Medicine at the University of Utah and the Director of the Pulmonary Function Laboratory at LDS Hospital, a laboratory that was internationally regarded for many contributions to understanding pulmonary function and pulmonary function testing. At this teaching laboratory where countless fellows, residents, and students learned the principles of pulmonary function testing, basic respiratory physiology, and how lung function tests could help them diagnose and treat lung disease, Dr. Crapo was a master teacher. Dr. Crapo received the 2006 Distinguished Scientist Honor Lecture award from the American College of Chest Physicians. We extend our condolences to the Crapo family.

This Month in CHEST: Editor’s Picks

Association of Psychological Disorders With 30-Day Readmission Rates in Patients With COPD. By Dr. G. Singh et al.

Brain Imaging for Staging of Patients With Clinical Stage IA Non-small Cell Lung Cancer in the National Lung Screening Trial: Adherence With Recommendations From the Choosing Wisely Campaign. By Dr. A. A. Balekian et al.

Stroke, Major Bleeding, and Mortality Outcomes in Warfarin Users With Atrial Fibrillation and Chronic Kidney Disease:

A Meta-Analysis of Observational Studies. By Dr. K. Dahal et al.

Contemporary Reviews in Critical Care Crises in Sickle Cell Disease. By Dr. E. M. Novelli and Dr. M. T. Gladwin.

Topics in Practice Management Developing an Interventional Pulmonary Service in a Community-Based Private Practice: A Case Study. By Ms. K. French et al.
SOUTHEASTERN OHIO
Holzer Health System is seeking a BE/BC Pulmonologist for an Office-Based practice at our main campus in Southeastern Ohio with a minimum of 10 days a month call, including one weekend.

Single hospital coverage, 266-bed regional acute referral hospital offering 24/7 hospitalist coverage and physically attached to the clinical practice in Gallipolis.

The salary is competitive and benefits are excellent!

- Guaranteed 2 year salary floor with immediate production incentive
- Signing bonus
- Educational loan repayment
- Relocation expense reimbursement
- Malpractice insurance provider by Holzer
- Life and Long Term Disability insurance provided by Holzer
- Attractive retirement options
- Starting at 5 weeks’ vacation; increases with tenure
- Up to 5 days off for Category 1 tested CME
- Health, dental and vision insurance available for provider and family

Contact Kenny Coughenough
Physician Recruiter at 740-446-5205 or kcoughen@holzer.org to find out more about this position!

CHARLOTTE, NC
Imminent Physician Opportunities – Charlotte, NC area!
CarolinaHealthCare System (CHS) is currently recruiting Pulmonary/Critical Care physicians for the Charlotte Metro region. CHS uses an integrated System approach to Pulmonary/Critical Care, combining established clinical practices with the innovative technology of a tele-ICU program. This is an opportunity to work for a progressive healthcare system and practice in a high-acuity environment with a large group of Pulmonary/Critical Care colleagues. Available positions offer a variety of opportunities in subspecialty disease specific care, interventional procedures, teaching and research. All candidates must be board certified/eligible in Pulmonary and/or Critical Care Medicine. Please send your CV to Elaine Haskell at elaine.haskell@carolinacare.org or call 704-631-1127.

ARIZONA
Tremendous job opportunity for a Board Certified Pulmonologist to join a well-established, busy, pulmonary office in a beautiful, sunny suburb of Metro Phoenix, Az. We have a multi-faceted practice that includes all facets of pulmonary medicine, including ICU, office and sleep medicine. Email CV and cover letter to: geri@azlungcenter.com

FRANKLIN COUNTY, OH
The Frankton Medical Center near Cincinnati, preferred but not required. Improve your lifestyle with regular work hours, no weekends, no nighttime call responsibilities. The opportunity is available if desired. Board eligible/certified in Pulmonary/Critical Care medicine is preferred but not required. Relocation assistance.

- Competitive salary, sign on bonus and 403(b) plus match, CME, malpractice insurance provided by Holzer
- Relocation expense reimbursement
- Signing bonus
- Immediate production incentive

Florida has an immediate opening for critical care/sleep medicine practice in Gallipolis, Ohio with a minimum of 10 days a month call, including one weekend.

The salary is competitive and benefits are excellent!

- Guaranteed 2 year salary floor with immediate production incentive
- Signing bonus
- Educational loan repayment
- Relocation expense reimbursement
- Malpractice insurance provider by Holzer
- Life and Long Term Disability insurance provided by Holzer
- Attractive retirement options
- Starting at 5 weeks’ vacation; increases with tenure
- Up to 5 days off for Category 1 tested CME
- Health, dental and vision insurance available for provider and family

Contact Kenny Coughenough
Physician Recruiter at 740-446-5205 or kcoughen@holzer.org to find out more about this position!
EBUS coding, asbestos, end-of-life care, respiratory therapy education, drowsy driving

Interventional Chest/ Diagnostic Procedures

New EBUS coding, CMS billing delays

On January 1, 2016, AMA CPT® created three new codes to describe endobronchial ultrasound (EBUS) procedures. These new codes were designed to better describe the actual service provided and incorporate the transbronchial needle aspiration (TBNA) into that service. CPT 31652 should be reported with aspiration of two or fewer mediastinal or hilar lymph node stations or structures, and CPT 31653 should be reported with aspiration of three or more mediastinal or hilar lymph node stations lymph node stations or structures. The older code for EBUS alone (31620) is now no longer available. The use of the radial probe EBUS now uses the ZZZ or add-on CPT code 31654 similar to the old CPT 31620 EBUS code. As an add-on, CPT 31654 must be used with another bronchoscopy code such as transbronchial biopsy (CPT 31628) or transbronchial needle aspiration when used in the periphery (31629). It is not appropriate to use CPT 31629 (TBNA) concurrently with the 31652 or 31653 CPT codes.

When these new codes were sent through the process of the National Correct Coding Initiative (NCCI), an error occurred such that some appropriate code pairs were deemed inappropriate by the software, resulting in claims being rejected, denied, or underpaid. ATS and CHEST notified the NCCI contractor and CMS, who agreed that there was, in fact, an error and it would be corrected as of April 1, 2016, since corrections get updated quarterly. It was recommended that all EBUS claims be held until April 1, 2016, or that members should be prepared to resubmit or ask for adjudication of improperly paid claims based on the updated NCCI edits.

Code descriptors below:

• 31652 with endobronchial ultrasound (EBUS) guided transtracheal and/or transbronchial sampling (eg, aspiration[s]/biopsy[ies], one or two mediastinal and/or hilar lymph node stations or structures
• 31653 with endobronchial ultrasound (EBUS) guided transtracheal and/or transbronchial sampling (eg, aspiration[s]/biopsy[ies]), 3 or more mediastinal and/or hilar lymph node stations or structures
• 31654 with transendoscopic endobronchial ultrasound (EBUS) during bronchoscopic diagnostic or therapeutic intervention(s) for peripheral lesion(s) (List separately in addition to code for primary procedure[s])

Dr. Thomas Gildea, FCCP
Steering Committee Member

Occupational and Environmental Health

Asbestos in Libby, MT

The Occupational and Environmental Steering Committee has interest in occupational and environmental exposures and their impact on economically disadvantaged populations. Exposure to vermiculite caused a public health emergency in Libby, MT.

There were 5.8 million tons of vermiculite mined and milled 6 miles from Libby from 1923 until 1990. Ore was contaminated with (26% by weight) Libby amphiboles (LA) asbestos. LA contained 6% tremolite asbestos, 84% winchite, and 11% richterite. Daily dust release from the mill of 5,000 to 10,000 pounds contaminated the periphery.

The mill began producing diatomite (50% by weight) Libby amphiboles (LA) asbestos. LA contained 6% tremolite asbestos, 84% winchite, and 11% richterite. Daily dust release from the mill of 5,000 to 10,000 pounds contaminated the periphery.

The full text of this document is available on the website 50NETWORKS.com.
Palliative, End-of-Life Care

Care when the “end” is not always clear

Patients with COPD experience disabling symptoms and emotional distress in the last year of life, rating quality of life (QoL) poor or worse than those with end-stage lung cancer (Gore et al. Thorax 2000;55[12]:1000). Only 20% have advance directives (Spathis et al. Int J Chron Obstruct Pulmon Dis. 2008;3[1]:11). Patients with COPD utilize more resource-intensive care (hospital/ICU stay and mechanical ventilation) in the last 90 days of life compared with patients with cancer or dementia (Teno et al. JAMA. 2013;309[5]:470).

Difficulties in end-of-life (Eol) experiences between patients with COPD and other patients were attributed to COPD’s disease trajectory. Patients with lung cancer or neuromuscular disorders can expect a period of functional stability, followed by sharp decline. COPD patients have progressive decline punctuated by acute exacerbations, leading to outcomes ranging from recovery to baseline to unexpected death. The unpredictable rate of decline and nature of acute exacerbations of chronic obstructive pulmonary disease (AE-COPD) result in overoptimistic prognostication and delay in initiating Eol care.

The 2011 Global Initiative on Chronic Obstructive Lung Disease (GOLD) marks a shift in the treatment paradigm: patients are risk stratified based on symptom burden, exacerbations, and airflow obstruction. Those with GOLD Group D have increased mortality risk and should be engaged in Eol discussions.

For patients experiencing AE-COPD, recent research identifies mortality risk factors: dyspnea at rest, radiographic consolidations, acidemia, atrial fibrillation (Echevarria et al. Thorax. 2016;71[2]:133), and eosinophilia (Bafadhel et al. Am J Respir Crit Care Med. 2011;184[6]:662).

We cannot predict which AE-COPD will be the final one for our patients; we can safeguard autonomy and QoL by educating patients about the nature of the disease and discussing advanced care planning when there are clear signals that the “end” is near.

Dr. Alisha Young
Steering Committee Physician-in-Training

Respiratory Care

May you live in interesting times!

This expression has never been a truer statement for our respiratory therapist (RT) colleagues. On January 6, 2016, the American Association of Respiratory Care (AARC) released a statement on RT education, stating, “Training and education for entry-to-practice as a respiratory therapist should be provided within programs awarding a bachelor’s or master’s degree in respiratory care ... all newly accredited respiratory care educational programs must award, as a minimum, the bachelor’s degree in respiratory care.” The Commission on Accreditation for Respiratory Care (CoARC) followed 3 weeks later with changes that would stop credentialing new associate degree training programs after January 1, 2018. Both actions move RT closer to the vision articulated by the AARC in its 2015 and Beyond Project.

These steps recognize the complexity of health care and the need for advanced technical and interpersonal skills as health care becomes more team based. RTs with advanced skills are increasingly needed for education, management, and advanced clinical practice. Current examples include COPD patient navigators and readmission reduction programs in which RTs are uniquely qualified to provide value to patients. State licensing boards are also recognizing the changing landscape. California and Ohio both now require the registered respiratory therapist (RRT) certificate for licensure and several other states are considering similar changes.

What does this mean for us? In the short term, most (currently 85%) new RTs will continue to graduate from associate degree programs. Additional education (degree completion, baccalaureate, and masters/doctoral training), however, will become increasingly important for RTs as they assume more diverse and important roles in our health-care system.

Dr. Kevin M. O’Neil, FCCP
Chair

Sleep Medicine

Sleep NetWork update

The Sleep NetWork had several late-breaking sessions at CHEST 2015 in Montréal, including a symposium reviewing the SERVE-HF Study results.

The study revealed an increased risk of cardiovascular death in symptomatic heart failure patients (NYHA II-IV, LVEF less than or equal to 45%) with central apnea (AHI greater than 15 with greater than 50% of central events and CAI greater than or equal to 10) when treated with adaptive serv ventilator (ASV) as compared with no ASV use (Cowie et al. N Engl J Med. 2015;373[12]:1095).

The discussion was centered on the clinical applicability of these results given several methodological and study design concerns, which affect the generalizability of the findings. Caution was recommended when considering ASV treatment for heart failure patients to ensure they don’t fall into this high-risk category. Future research will help delineate the best treatment approaches for these patients.

More recently, the Sleep NetWork endorsed a consensus statement by the National Sleep Foundation (NSF) on drowsy driving.

Driving while sleep-deprived yields a performance similar to driving while under the influence of alcohol (Dawson et al. Nature. 1997;388:6639). The NSF Drowsy Driving Consensus Work Group concluded that drivers who have slept for 2 hours or less in the preceding 24 hours are not fit to operate a motor vehicle. This statement will have implications for commercial drivers, shift workers, and even clinicians.

Dr. Aneesa Das, FCCP
Steering Committee Chair
Dr. Ana Krieger, FCCP
Steering Committee Member

INDEX OF ADVERTISERS

Actelion Pharmaceuticals US, Inc. 11
Allergan 37
AstraZeneca 8-9
Boehringer Ingelheim Pharmaceuticals, Inc. 40-44
Boehringer Ingelheim Pharmaceuticals, Inc. 38-40
Boehringer Ingelheim Pharmaceuticals, Inc. 9-10
Boehringer Ingelheim Pharmaceuticals, Inc. 30-31
Boehringer Ingelheim Pharmaceuticals, Inc. 13-14
Bristol-Myers Squibb Company 32-33
Cheil USA, Inc. 12-13
Cipla Inc. 2-3
Eli Lilly & Co. 19-20
Fresenius 30-31
Genentech USA, Inc. 2-3
Genentech USA, Inc. 19-20
Genentech USA, Inc. 10-11
Lundbeck 30-31
MedBridge 30-31
Midmark 30-31
Genentech USA, Inc. 2-3
Genentech USA, Inc. 19-20
United Therapeutics Corporation 30-31
History's greatest instruments really get the blood moving.