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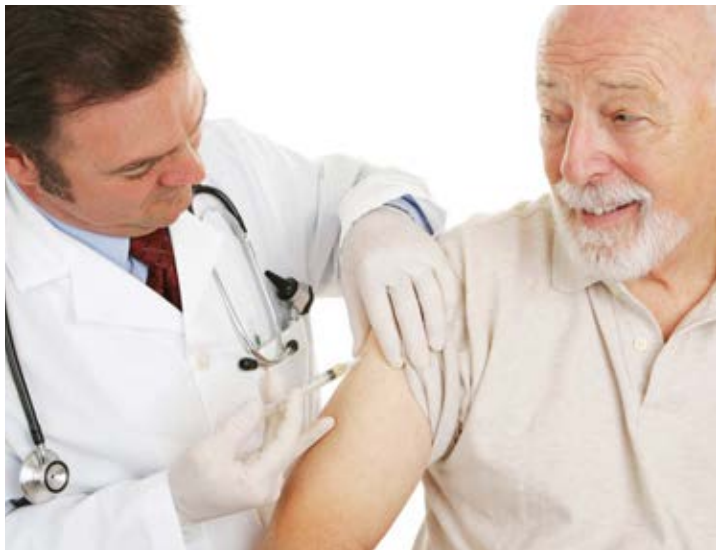

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In adults 65 and older, PCV13 was 75% effective for preventing vaccine-type strains of invasive pneumococcal disease.

PCV13 efficacy in elderly confirmed

BY MARY ANN MOON
Frontline Medical News

The 13-valent polysaccharide conjugate vaccine showed "significant efficacy" against vaccine-type strains of community-acquired pneumonia and vaccine-type invasive pneumococcal disease among elderly participants in a large clinical trial in the Netherlands.

The PCV13 vaccine's efficacy in adults aged 65 years and older has never been determined until now.

It became possible to assess efficacy in this age group when a serotype-specific urinary antigen detection assay was developed. The assay can identify *Streptococcus pneumonia* polysaccharides in the urine of patients suspected of having pneumonia and avoids the need to isolate the organism in culture, Dr. Marc J.M. Bonten of Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht (the Netherlands), and his associates wrote.

The researchers used the assay to assess PCV13 efficacy in 84,496 older adults who were randomly assigned to receive active vaccine (42,240 participants) or placebo (42,256) and followed for a mean of 4 years in the trial, which was spon-

See **PCV13** • *page 10*

Reslizumab aces trials in asthma with eosinophilia

Exacerbations halved with reslizumab.

BY BRUCE JANCIN
Frontline Medical News

HOUSTON – Reslizumab, a next-generation molecular-based asthma therapy, achieved its primary and secondary endpoints and demonstrated favorable safety in patients with moderate to severe asthma and eosinophilia in two pivotal clinical trials.

"We believe that reslizumab is an effective therapy for controlling asthma in patients with elevated blood eosinophils who are inadequately controlled on medium- to high-dose inhaled corticosteroid–based regimens," said Dr. Mario Castro, FCCP, who presented the results of two phase III studies at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

The frequency of clinical asthma exacerbations was reduced by more than half in reslizumab-treated patients, compared with controls in the two year-long studies. In addition, the reslizumab group experienced an early improvement in lung function as expressed in forced expiratory volume in 1 second (FEV_1) that was sustained throughout the year-long trials, as well as improvements in other measures of

See **Reslizumab** • *page 7*

INSIDE

Panel backs ICS/LABA for adults only

BY ELIZABETH MECHCATIE
Frontline Medical News

GAITHERSBURG, MD. – A Food and Drug Administration advisory panel supported approval of a fluticasone and vilanterol combination to treat asthma in adults – but the majority voted against approval for adolescents, citing a need for more safety and effectiveness data in that population.

GlaxoSmithKline has proposed that two fixed-dose combinations, 100 mcg or 200 mcg of the inhaled corticosteroid (ICS) fluticasone with 25 mcg of the long-acting beta-agonist (LABA) vilanterol in a dry powder inhaler, be approved for maintenance treatment of asthma in patients age 12 years and older, administered once per day.

The FDA approved the 100-mcg/25-mcg dose in 2013 to treat chronic obstructive pulmonary disease; GSK markets it as Breo Ellipta. To earn an asthma indication, the company submitted data from four studies,

See **ICS/LABA** • *page 47*

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Reduce lung function decline

Delay IPF Progression with Esbriet

Indication

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

Select Important Safety Information

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

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

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

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

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

Introducing Esbriet® (pirfenidone) capsules 267 mg

Proven to delay progression in IPF[2]

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

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

*The efficacy of Esbriet was evaluated in three phase 3, randomized, double-blind, placebo-controlled trials. In ASCEND, 555 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo for 52 weeks. Eligible patients had %FVC between 50%-90% and DL_{CO} between 30%-90%. The primary endpoint was change in %FVC from baseline to week 52.

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

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

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

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

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

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

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

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

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

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

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Esbriet®
(pirfenidone) capsules 267 mg

Rx only

BRIEF SUMMARY

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Elevated Liver Enzymes

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

Photosensitivity Reaction or Rash

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

Gastrointestinal Disorders

In the clinical studies, gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastro-esophageal reflux disease, and abdominal pain were more frequently reported by patients in the ESBRIET treatment groups than in those taking placebo. Dosage reduction or interruption for gastrointestinal events was required in 18.5% of patients in the 2403 mg/day group, as compared to 5.8% of patients in the placebo group; 2.2% of patients in the ESBRIET 2403 mg/day group discontinued treatment due to a gastrointestinal event, as compared to 1.0% in the placebo group. The most common (>2%) gastrointestinal events that led to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. The incidence of gastrointestinal events was highest early in the course of treatment (with highest incidence occurring during the initial 3 months) and decreased over time. Dosage modifications may be necessary in some cases of gastrointestinal adverse reactions *[see Dosage and Administration section 2.3 in full Prescribing Information]*.

ADVERSE REACTIONS

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

- Liver Enzyme Elevations *[see Warnings and Precautions]*
- Photosensitivity Reaction or Rash *[see Warnings and Precautions]*
- Gastrointestinal Disorders *[see Warnings and Precautions]*

Clinical Trials Experience

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

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

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

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

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

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

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

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

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

Postmarketing Experience

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

Blood and Lymphatic System Disorders
Agranulocytosis

Immune System Disorders
Angioedema

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

DRUG INTERACTIONS

CYP1A2 Inhibitors

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

Strong CYP1A Inhibitors

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

Moderate CYP1A Inhibitors

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

Concomitant CYP1A2 and other CYP Inhibitors

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

CYP1A2 Inducers

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: **Pregnancy Category C.**

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

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

ESBRIET® (pirfenidone)

Hepatic Impairment

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

The safety, efficacy, and pharmacokinetics of ESBRIET have not been studied in patients with severe hepatic impairment. ESBRIET is not recommended for use in patients with severe (Child Pugh Class C) hepatic impairment *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*.

Renal Impairment

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

Smokers

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

OVERDOSAGE

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

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

PATIENT COUNSELING INFORMATION

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

Liver Enzyme Elevations

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

Photosensitivity Reaction or Rash

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

Gastrointestinal Events

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

Smokers

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

Take with Food

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

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

INTERMUNE®

Respiratory harm declined with e-cigarette switch

BY BRUCE JANCIN
Frontline Medical News

HOUSTON – Asthmatic smokers who switched to electronic cigarettes showed evidence suggestive of respiratory harm reversal in a retrospective pilot study.

"Electronic cigarette use improves respiratory physiology and subjective asthma outcomes in asthmatic smokers," Dr. Cristina Russo said at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

She said that her small retrospective study is the first to examine the respiratory health impact of a switch to e-cigarettes by asthmatic smokers.

Each of the objective and subjective measures of asthma status evaluated in the study showed statistically significant improvement 1 year after patients adopted e-cigarettes, and the e-cigarette users' consumption of conventional cigarettes dropped precipitously, reported Dr. Russo of the University of Catania (Italy).

She and her colleagues in the university asthma clinic have taken to suggesting the use of e-cigarettes to their asthmatic smokers who haven't benefited from or aren't interested in trying the more conventional approaches to smoking cessation or reduction, including medications. While abstinence from smoking is best, the available evidence indicates e-cigarettes are at least 95% less harmful than conventional cigarettes in the general population, she said.

The study included 18 smokers with mild to moderate asthma who began to use e-cigarettes and underwent spirometry and other testing at baseline and 6 and 12 months of follow-up.

Ten patients switched over to e-cigarettes exclusively; the other eight used conventional and e-cigarettes.

Among the study highlights: The mid-range forced expiratory flow (25%-75%) increased from 2.75 L/sec to 3.11 L/sec. And patients' mean self-reported conventional cigarette consumption dropped from 21.9 per day at baseline to 5 at 6 months and 3.9 per day at 12 months.

Dr. Russo's presentation sparked vigorous audience discussion. Several physicians cited a Centers for Disease Control and Prevention warning about the unknowns regarding e-cigarette safety, but others defended the "lesser of two evils" approach.

Dr. Russo called smoking and asthma "a dangerous liaison." Smoking accelerates asthma patients' decline in lung function, worsens persistent airways obstruction, and increases insensitivity to corticosteroids.

bjancin@frontlinemedcom.com

VITALS

Key clinical point: Asthmatic smokers who switched to electronic cigarettes showed significant 1-year improvements in lung function, methacholine-provoked airway hyperresponsiveness, and asthma-related quality of life.

Major finding: After use of e-cigarettes was initiated, self-reported daily consumption of conventional cigarettes fell from a mean of 21.9 per day at baseline to 5.0 at 6 months and 3.9 at 12 months of follow-up.

Data source: This retrospective pilot study included 18 asthmatic smokers.

Disclosures: The study was supported by a university grant and the Italian League Against Smoking. The presenter reported having no financial conflicts.

Salutary changes following switch to e-cigarettes

	Baseline	12 months
Forced expiratory volume in 1 sec (FEV_1)	3.3 L/sec	3.4 L/sec
Forced vital capacity	4.28 L	4.43 L
Midrange forced expiratory flow	2.75 L/sec	3.11 L/sec
Methacholine concentration required to produce a 20% fall in FEV_1 from baseline	1.24 mg/mL	2.56 mg/mL
Asthma Control Questionnaire score	2.03	1.43
Mean conventional cigarettes per day	21.9	3.9

Note: Based on data from 18 smokers with mild to moderate asthma.

Source: Dr. Russo

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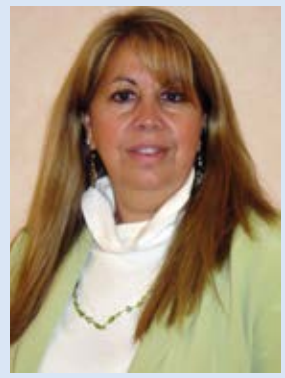

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Exacerbations were halved

Reslizumab *from page 1*

asthma control, including quality of life, Dr. Castro, professor of pulmonary and critical care medicine and pediatrics at Washington University in St. Louis, said.

Elevated blood and sputum levels of eosinophils define an asthma phenotype at increased risk for serious asthma exacerbations. Reslizumab is a humanized monoclonal antibody that binds circulating interleukin-5 and prevents binding to the IL-5 receptor, thereby disrupting eosinophil production and function.

Dr. Castro presented two identically designed phase III, double-blind, placebo-controlled, 12-month studies totaling 953 adolescents and adults. They were randomized to intravenous reslizumab at 3 mg/kg or placebo every 4 weeks for a year.

The primary endpoint was frequency of clinical asthma exacerbations (CAEs), an independently adjudicated composite outcome that required an episode featuring an increase in corticosteroids, an asthma-related ER visit or unscheduled office visit, evidence of asthma worsening in the form of at least a 20% drop from baseline in FEV_1 or a 30% reduction in peak expiratory flow rate on 2 consecutive days, and worsening clinical symptoms.

Participants averaged two CAEs during the year prior to enrollment. The placebo-treated controls maintained that event rate during the two year-long studies, while the reslizumab-treated patients experienced 50% and 59% reductions relative to controls ($P < .0001$).

Reslizumab also increased the time to first CAE. In the two trials, 61% and 73% of reslizumab-treated patients didn't develop a single CAE during 52 weeks, compared with 44% and 52% of controls.

The more CAEs a patient had in the year prior to enrollment, the greater the magnitude of benefit with reslizumab. While the relative risk reduction was 54%, compared

Continued on following page

VIEW ON THE NEWS

Dr. Daniel Ouellette, FCCP, comments: Asthma is a highly prevalent disease in urban America and one that remains challenging to treat. The patients attending my downtown clinic have persistent asthma complicated by obesity, pregnancy, and active smoking. Their condition is exacerbated because of substandard insurance, substandard housing, and inadequate medical follow-up. The monoclonal IL-5 antibody reslizumab offers promise, but the glowing reports raise questions for me. I know that at least two other companies are developing anti-IL-5 monoclonals. Will they be different from reslizumab? Will an urban population benefit to the same degree as the population in these reports? Will my patients have access to these drugs, or will we be mired in a world of unaffordable co-pays and declined pre-authorizations?

Continued from previous page

with placebo, it climbed to 64% in patients with four or more CAEs in the previous year.

FEV_1 improved after the first dose of reslizumab. Placebo-subtracted gains of 0.126 L in one trial and 0.09 L in the other were sustained throughout the 52 weeks.

The reslizumab group also outperformed controls in terms of Asthma Control Questionnaire scores and Asthma Quality of Life Questionnaire scores. For example, 74% and 73% of reslizumab-treated patients in the two studies experienced at least a 0.5-point improvement in the AQLQ, which is considered the minimal clinically important difference, compared with 65% and 62% of controls.

Study discontinuation due to adverse events occurred in 2% of patients on reslizumab, with worsening asthma the No. 1 reason.

Two patients on reslizumab had anaphylactoid reactions; neither required epinephrine. Three percent of reslizumab-treated patients developed low-titer, generally transient antidrug antibodies that didn't affect eosinophil levels, which dropped with the first dose of reslizumab and stayed low throughout the studies.

Reslizumab is one of a cluster of novel agents in development for se-

vere or treatment-resistant asthma. These are targeted therapies directed at specific patient phenotypes. Biomarkers such as eosinophilia provide guidance as to the specific asthmatic inflammatory pathways involved.

In an interview, Dr. James E. Gern, who wasn't involved in the reslizumab studies, said the various severe asthma phenotypes account for a relatively small proportion of the total asthma population, but a tremendously disproportionate amount of health care utilization.

These new medications will "be indicated for a relatively small number of people. But for those people, it'll make a huge difference because of the huge burden that severe asthma has on quality of life," said Dr. Gern, professor of pediatrics at the University of Wisconsin, Madison.

The two reslizumab studies were sponsored by Teva. Dr. Castro is on the company's speakers' bureau and receives grants from more than a dozen companies as well as from the National Institutes of Health and Centers for Disease Control and Prevention.

The study results are published online (Lancet Respir. Med. 2015 [doi.org/10.1016/S2213-2600(15)00042-9]).

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Self-reported penicillin allergy may be chronic urticaria

BY DEEPAK CHITNIS
Frontline Medical News

HOUSTON – Patients with self-reported penicillin allergy may actually have chronic urticaria, Dr. Susanna G. Silverman, of the University of Pennsylvania, Philadelphia reported at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

A retrospective chart review of 1,419 patients with self-reported penicillin allergy revealed that 12% had a diagnosis of chronic urticaria, a significantly higher percentage than the typical prevalence range of 0.5%-5% for chronic urticaria in the general population. Of the 175 patients who had chronic urticaria, 84% were female, and 53% were white.

The study included patients at the University of Pennsylvania's allergy and immunology clinic who self-reported penicillin allergy from June 2007 to August 2014.

Patients were identified as having penicillin allergy if penicillin, amoxicillin, amoxicillin-clavulanate, or piperacillin-tazobactam were present on the allergy list of their medical records.

Dr. Silverman then identified all patients from that group who also received a diagnosis of urticaria – a total of 343 patients – then narrowed the list to those who were diagnosed with chronic urticaria or the presence of urticaria for at least 6 weeks.

"We think it's important for physicians to think about this and to ask patients about symptoms of chronic urticaria when they report penicillin allergy," Dr. Silverman noted, "to better determine what is truly penicillin allergy versus simply chronic urticaria symptoms."

Dr. Silverman did not report any financial disclosures.

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Two new strains advised for 2015-2016 flu vaccine

BY ELIZABETH MECHCATIE
Frontline Medical News

SILVER SPRING, MD. – Two components of the trivalent and quadrivalent influenza vaccines used during the current season should be replaced for the 2015-2016 vaccine, including the influenza AH3N2) component, a Food and Drug Administration advisory panel has stated.

During the current season, most of the influenza activity in the United States has been due to influenza A (H3N2), and more than two-thirds of the A (H3N2) viruses tested at the Centers for Disease Control and Prevention have "drifted" from the A (H3N2) strain included in the current vaccines, reducing their effectiveness.

The FDA's Vaccines and Related Biologicals Products Advisory Committee voted at a meeting March 4 to recommend that the following viruses be used for the 2015-2016 trivalent vaccine: an A/California/7/2009 (H1N1)pdm09-like virus; an A/Switzerland/9715293/2013 (H3N2)-like virus; and a B/Phuket/3073/2013-like virus (B/Yamagata lineage).

The A (H3N2) strain and the B/Yamagata lineage strain would replace the strains in the current vaccine.

The committee recommended a B/Brisbane/60/2008-like virus (B/Victoria lineage) for the second influenza B strain in the quadrivalent vaccine, which is included in the current quadrivalent vaccine.

The panel votes separately on the strains; all votes were unanimous, except for the vote on the B/Yamagata lineage strain in the trivalent vaccine, which was supported by a 14-1 vote.

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The FDA panel's recommendation is the same as the recommendation made recently by the World Health Organization for next season's influenza vaccines in the Northern Hemisphere.

Every year, the FDA panel meets at this time and considers the WHO recommendation, as well as information that includes influenza surveillance and epidemiology data in North America and worldwide.

Hospitalization rates for laboratory-confirmed influenza this season have been markedly higher among people aged 65 years and older, compared with younger age groups.

In late February, the preliminary estimate of hospitalizations in this age group was 51.7 cases per 100,000 people, compared with about 27 per 100,000 during the last season.

This is the highest rate recorded for this age group since surveillance began during the 2005-2006 season, according to Dr. Lisa Grohskopf of the epidemiology & prevention branch in the CDC's influenza division.

When asked why the hospitalization rate has been so high among the elderly, Dr. Grohskopf said that A (H3N2)–predominant seasons tend to be associated with more severe disease, and vaccine efficacy this season was reduced.

Updated estimates of the current vaccine effectiveness against influenza A (H3N2) viruses, provided by the CDC is 18%. For all influenza viruses overall, estimated effectiveness is 19%, indicating that the flu vaccine reduced a person's risk of having to seek medical care at a doctor's office for flu illness by 19%, according to the update.

During seasons when the vaccine is a good match for circulating viruses, vaccine effectiveness is in the 60% range, according to speakers at the FDA panel meeting.

The FDA usually follows the recommendations of its panel members. None of the panelists had disclosures.

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Vaccine efficacy confirmed

PCV13 *from page 1*

sored by Pfizer Inc.

In the per-protocol analysis, vaccine efficacy was 46% for preventing a first episode of vaccine-type community-acquired pneumonia, 45% for preventing nonbacteremic and noninvasive vaccine-type community-acquired pneumonia, and 75% for preventing vaccine-type invasive pneumococcal disease.

Evidence of the vaccine's efficacy became apparent shortly after vaccination occurred and persisted throughout the duration of the study.

There was no evidence of any safety concerns in the patients who received the active vaccine, wrote Dr. Bonten and his associates (N. Engl. J. Med. 2015 March 19 [doi:10.1056/NEJMoa1408544]).

The PCV13 vaccine did not show efficacy in preventing death from any cause, but the number of deaths associated with pneumococcal disease in this study was too small to allow a meaningful analysis of this outcome, Dr. Bonten and his associates noted.

VITALS

Key clinical point: The 13-valent pneumococcal polysaccharide conjugate vaccine is effective against community-acquired pneumococcal pneumonia in adults aged 65 years and older.

Major finding: Vaccine efficacy was 46% for preventing a first episode of vaccine-type strains of community-acquired pneumonia, 45% for preventing nonbacteremic and noninvasive vaccine-type strains of community-acquired pneumonia, and 75% for preventing vaccine-type strains of invasive pneumococcal disease.

Data source: An industry-sponsored randomized placebo-controlled double-blind trial involving 84,496 Dutch adults aged 65 years and older followed for a mean of 4 years after vaccination.

Disclosures: Pfizer sponsored the study. Dr. Bonten and several associates reported ties to Pfizer, and his associates also reported ties to GlaxoSmithKline, Roche, and Novartis.

FDA's app provides real-time drug shortage information

BY ELIZABETH MECHCATIE
Frontline Medical News

A mobile app that provides up-to-date information on drug shortages has been launched by the Food and Drug Administration.

The mobile application is "specifically designed to speed public access to valuable information about drug shortages," namely, current and resolved drug shortages and discontinuations of drug shortages, according to the FDA statement.

One can search by a drug's generic name, active ingredient, or therapeutic category, and can use the app to report a drug shortage or a supply issue to the FDA.

The app provides "easier and faster access to important drug shortage information," Capt. Valerie Jensen, R.Ph., associate director of the drug shortages program in the FDA's Center for Drug Evaluation and Research, said in the statement. "Health care professionals and pharmacists need real-time information about drug shortages to make treatment decisions."

©Nick Smith/Stockphoto

The app is free and can be downloaded via iTunes for Apple devices and the Google Play store for Android devices, searching for "FDA Drug Shortages."

More information is available on the FDA's web site at http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm.

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PULMONARY PERSPECTIVES: ECMO – The new state of the art?

BY DR. PAUL C. SAUNDERS

The treatment of severe cardiac and respiratory failure has historically carried a high mortality – up to 50% in some series. Since the 1970s, extracorporeal membrane oxygenation (ECMO) has been used to treat patients with refractory shock, but until recently excessive morbidity and technical challenges left ECMO as a therapy offered to a limited group of patients at select centers. Over the past few years, a unique confluence of events, including the H1N1 pandemic, sparked the resurgence of ECMO in ICUs around the world. Since this time, interest in the use of ECMO in a variety of clinical settings has continued to grow (MacLaren et al. *Intensive Care Med.* 2012;38[2]:210). More centers are now using ECMO to support patients with a growing set of indications, and more reports about ECMO are added to the literature each year. Despite its rapid growth, uncertainty persists regarding the ultimate role of ECMO in the treatment of severe cardiopulmonary failure, given the limited data available (Leligdowicz et al. *Curr Opin Crit Care.* 2015;21[1]:13).

ECMO supports the patient by circulating venous blood through an extracorporeal circuit consisting of a blood pump and an oxygenator, which adds oxygen and removes carbon dioxide. The oxygenated blood is then returned back to the venous circulation (venovenous ECMO) or the arterial circulation (venoarterial ECMO). Venovenous ECMO is used to provide respiratory support, whereas venoarterial ECMO, as it is providing pressurized blood flow to the systemic circulation, can provide full cardiopulmonary support. Cannula locations are dependent on the type of support needed. Venovenous ECMO is frequently accomplished by draining blood from the inferior vena cava via the femoral vein and returning oxygenated blood to the right atrium via the internal jugular vein. A newer, dual-lumen cannula can drain blood from the inferior vena cava and return it to the right atrium as well, eliminating the need for lower body cannulation and allowing for better patient mobilization. One of the most important aspects of venovenous ECMO is lung rest, as it facilitates aggressive lung protective strategies that can allow lung injury to heal while minimizing barotrauma (Brodie et al. *N Engl J Med.* 2011;365[20]:1905).

Venoarterial ECMO is most commonly achieved with femoral venous drainage and femoral arterial return, as these cannulae can be deployed rapidly in any location. Alternatively, oxygenated blood can be returned to the axillary artery, which has the advantage of antegrade flow, which can be beneficial in providing the most physiologic means of support. Venoarterial ECMO is powerful in cases of profound cardiogenic shock, as flow rates well over 5 L can be achieved. Venoarterial ECMO can also be a useful tool as a "bridge to decision" device to stabilize patients until they can safely undergo more definitive left ventricular assist device (LVAD) implantation (Takayama et al. *J Heart Lung Transplant.* 2013;32[1]:106).

The earliest ECMO circuits were essentially repurposed heart-lung machines. When used to support patients for periods longer than a cardiac bypass run, they had shortcomings. They were labor-intensive to set up and manage in the ICUs, and therefore, required a perfusionist at the bedside. The oxygenators used had a relatively short lifespan and were subject to clotting, air embolization, and unpredictable failure. Similarly, roller pumps produced excessive damage to blood elements, were challenging to maintain, and were laborious to set up and prime (Leligdowicz et al. *Curr Opin Crit Care.* 2015;21[1]:13). Morbidity was high and complications, including bleeding, stroke, and infections, were common.

A newer, dual-lumen cannula can drain blood from the inferior vena cava and return it to the right atrium as well, eliminating the need for lower body cannulation and allowing for better patient mobilization.

Published reports from the early ECMO experience were troubling and did little to encourage wider adoption of ECMO in cardiopulmonary failure. In a controlled, multicenter trial of ECMO for acute respiratory distress syndrome (ARDS) published in *JAMA* in 1979, 90 patients were randomized to ECMO vs conventional therapy. ECMO did not improve survival; in fact, both groups had excessive mortality (>80%) (Zapol et al. *JAMA.* 1979;242[20]:2193). However, these results probably reflect the state of ARDS treatment and the primitive ECMO circuits of the era rather than the efficacy of ECMO support (Del Sorbo et al. *Lancet Respir Med.* 2014;2[2]:154).

In the face of negative reports, the use of ECMO was stagnant for roughly 30 years, until key events in the late 2000s caused a paradigm shift. Cardiopulmonary bypass technology had advanced significantly, with a new class of smaller, more efficient centrifugal pumps that are not only more resistant to clotting but also produce less hemolysis by limiting blood contact with foreign surfaces. Their operation was more intuitive, set-up time was shorter, and they required less priming volume.

Similar advancements had been made in oxygenators, with the rise of polymethylpentene hollow-fiber oxygenators that boasted a lifespan measured in weeks, not days. More resistant to thrombosis and foaming, they were safer to maintain over extended periods and also produced less inflammatory response (Leligdowicz et al. *Curr Opin Crit Care.* 2015;21[1]:13). Due to these advances, smaller, percutaneous ventricular assist devices were introduced for acute circulatory support, promising faster, easier implementation of support for critically ill patients. In addition, complications were minimized, with improvements in bleeding and neurologic adverse events.

These advances were reflected in the next multicenter trial of ECMO for ARDS, the CESAR trial, published in *Lancet* in 2009. Performed in the United Kingdom, 180 patients with ARDS were randomized to conventional therapy vs ECMO support. While serious concerns have been raised about the study's methodology, use of ECMO was found to significantly improve survival (Peek et al. *Lancet.* 2009;374[9698]:1351).

In April 2009, cases of influenza A (H1N1) were initially reported in Mexico, and, over the next few months, had spread rapidly across the globe. By 2010, the Centers for Disease Control and Prevention had estimated approximately 60 million cases of influenza A (H1N1) in the United States, leading to over 270,000 hospitalizations and over 12,000 deaths.

Especially frightening to those working in ICUs, 87% of H1N1 deaths occurred in patients under 65 years of age. Working adults had an 8- to 12-times greater risk of hospitalization and death compared with seasonal influenza over the past 25 years (Shrestha et al. *Clin Infect Dis.* 2011;52(suppl 1):S75). Many of these younger patients presented with rapidly progressive ARDS, and many were treated aggressively using ECMO support, with favorable outcomes, as first reported in Australia and New Zealand (ANZ ECMO Influenza Investigators. *JAMA.* 2009;302[17]:1888). As a result, worldwide use of ECMO spiked in response to the influenza A (H1N1) pandemic. Over time, centers gained experience using these safer, more rapidly deployable, and more easily transportable ECMO circuits (Combes et al. *Am J Respir Crit Care Med.* 2014;190[5]:488).

Worldwide use of ECMO spiked in response to the influenza A (H1N1) pandemic. Over time, centers gained experience using these safer, more rapidly deployable, and more easily transportable ECMO circuits.

Since 2009, the use of ECMO has continued to grow. Data from the Extracorporeal Life Support Organization (ELSO) show over 250 ECMO centers worldwide, with over 5,000 total ECMO cases per year.

PubMed citations also show a dramatic increase in scholarly reports related to ECMO from the late 2000s, continuing to rise into 2015.

The increased use of the technology has also expanded the indications for ECMO support. Venovenous ECMO is most commonly used to support patients with respiratory failure due to ARDS but can also support patients waiting for lung transplantation, suffering posttransplant graft dysfunction, or even patients with postpneumonectomy ARDS.

The Extracorporeal Life Support Organization (ELSO) guidelines outline triggers for venovenous ECMO, including: hypoxic respiratory failure when risk of mortality is >80%, carbon dioxide retention (CO_2) on mechanical ventilation despite high plateau pressures, and severe air leak syndromes (*ELSO Guidelines*, December 2013. www.elso.org).

Venoarterial ECMO is used in cardiogenic shock from acute coronary syndromes, acute decompensated heart failure, myocarditis, pulmonary embolism, postcardiotomy shock, and primary graft failure after cardiac transplantation. Some centers

Continued on page 14

VIBATIV is the *only* once-daily bactericidal antibiotic with a dual mechanism of action indicated for infections due to MRSA[1]

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INDICATION

VIBATIV is indicated for the treatment of adult patients with hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP), caused by susceptible isolates of *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates). VIBATIV should be reserved for use when alternative treatments are not suitable.

VIBATIV is indicated for the treatment of adult patients with complicated skin and skin structure infections (cSSSI) caused by susceptible isolates of the following Gram-positive microorganisms:

- *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates)
- *Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus anginosus* group (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), or
- *Enterococcus faecalis* (vancomycin-susceptible isolates only)

Combination therapy may be clinically indicated if the documented or presumed pathogens include Gram-negative organisms.

Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify the causative pathogens and to determine their susceptibility to telavancin. VIBATIV may be initiated as empiric therapy before results of these tests are known. To reduce the development of drug-resistant bacteria and maintain the effectiveness of VIBATIV and other antibacterial drugs, VIBATIV should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Available in two strengths: 250 mg and 750 mg[1]

VIBATIV® (telavancin) for injection

IMPORTANT SAFETY INFORMATION

Mortality
Patients with pre-existing moderate/severe renal impairment (CrCl ≤50 mL/min) who were treated with VIBATIV for hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia had increased mortality observed versus vancomycin. Use of VIBATIV in patients with pre-existing moderate/severe renal impairment (CrCl ≤50 mL/min) should be considered only when the anticipated benefit to the patient outweighs the potential risk.

Nephrotoxicity
New onset or worsening renal impairment occurred in patients who received VIBATIV. Renal adverse events were more likely to occur in patients with baseline comorbidities known to predispose patients to kidney dysfunction and in patients who received concomitant medications known to affect kidney function.

Monitor renal function in all patients receiving VIBATIV prior to initiation of treatment, during treatment, and at the end of therapy. If renal function decreases, the benefit of continuing VIBATIV versus discontinuing and initiating therapy with an alternative agent should be assessed.

Fetal Risk
Women of childbearing potential should have a serum pregnancy test prior to administration of VIBATIV. Avoid use of VIBATIV during pregnancy unless the potential benefit to the patient outweighs the potential risk to the fetus. Adverse developmental outcomes observed in three animal species at clinically relevant doses raise concerns about potential adverse developmental outcomes in humans. If not already pregnant, women of childbearing potential should use effective contraception during VIBATIV treatment.

Contraindication
VIBATIV is contraindicated in patients with a known hypersensitivity to the drug.

Hypersensitivity Reactions
Serious and potentially fatal hypersensitivity reactions, including anaphylactic reactions, may occur after first or subsequent doses. VIBATIV should be used with caution in patients with known hypersensitivity to vancomycin.

Geriatric Use
Telavancin is substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in this age group.

Infusion Related Reactions
VIBATIV is a lipoglycopeptide antibacterial agent and should be administered over a period of 60 minutes to reduce the risk of infusion-related reactions. Rapid intravenous infusions of the glycopeptide class of antimicrobial agents can cause "Red-man Syndrome"-like reactions including: flushing of the upper body, urticaria, pruritus, or rash.

QTc Prolongation
Caution is warranted when prescribing VIBATIV to patients taking drugs known to prolong the QT interval. In a study involving healthy volunteers, VIBATIV prolonged the QTc interval. Use of VIBATIV should be avoided in patients with congenital long QT syndrome, known prolongation of the QTc interval, uncompensated heart failure, or severe left ventricular hypertrophy.

Most Common Adverse Reactions
The most common adverse reactions (greater than or equal to 10% of patients treated with VIBATIV) were taste disturbance, nausea, vomiting, and foamy urine.

For full Prescribing Information, including Boxed Warning and Medication Guide in the US, please visit www.VIBATIV.com.

References: 1. VIBATIV® (telavancin) Prescribing Information. Theravance Biopharma Antibiotics, Inc. March 2014. **2.** Draghi DC, et al. Comparative surveillance study of telavancin activity against recently collected Gram-positive clinical isolates from across the United States. *Antimicrob Agents and Chemother.* 2008;52:2383-2388. **3.** Draghi DC, et al. *In vitro* activity of telavancin against recent Gram-positive clinical isolates: results of the 2004-05 Prospective European Surveillance Initiative. *J Antimicrob Chemother.* 2008;62:116-121. **4.** Data on file. Theravance Biopharma Antibiotics, Inc.

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Continued from page 11

have been aggressively using ECMO support in patients suffering cardiac arrest from myriad causes, with so-called "E-CPR" (Lawler et al. *Circulation.* 2015;131[7]:676).

The rapid deployment possible with the latest generation of ECMO technology has given rise to specialized ECMO teams within hospitals, similar to traditional code teams, which can be quickly summoned to evaluate and offer mechanical support if indicated. Given the rapid priming and percutaneous deployment of the modern ECMO circuit, patients are more frequently placed on ECMO outside of the operating room, where cannulation was traditionally performed. Patients can be easily and safely placed on ECMO in varied locations throughout the hospital, including the ED, ICU, and the cardiac catheterization laboratory. The growth of ECMO teams has facilitated closer working relationships between critical care specialists, pulmonologists, surgeons, and cardiologists, as well as other staff members (nurses, respiratory therapists, etc) critical to a successful program.

The greater accessibility of ECMO has led to more hospitals seeking to offer the therapy to their critically ill patients. What was once limited to a select group of tertiary medical centers is now offered at a wider range of facilities (Combes et al. *Am J Respir Crit Care Med.* 2014;190[5]:488).

Despite the many improvements in the technical aspects of ECMO support, the available data are still limited. While the older randomized clinical trials failed to show any benefit from ECMO support, the CESAR trial, while its methodology has been questioned, did demonstrate a survival benefit in patients with ARDS. However, the remaining data to support the use of ECMO comes from cohort studies and case series. The ongoing EOLIA trial (Extracorporeal Membrane Oxygenation to Rescue Lung Injury in Severe Acute Respiratory Distress Syndrome, NCT01470703) will serve as an international, randomized, multicenter investigation of venovenous ECMO for the treatment of ARDS. Until the data are available, the expansion of ECMO must be tempered with caution as evidence is still lacking on which patients truly benefit from ECMO (Tramm et al. *Cochrane Database Syst Rev.* 2015;1:CD010381).

Venovenous ECMO is most commonly used to support patients with ARDS but can also support patients waiting for lung transplantation, suffering posttransplant graft dysfunction, or even patients with postpneumonectomy ARDS.

Technologic advances have made ECMO therapy widely adaptable to many clinical situations and easily available at more medical centers. In contrast to the circuits of the past, current ECMO support is easier to implement and safer to operate.

As more data are collected, a more critical evaluation of the role of ECMO in the treatment of cardiopulmonary failure will finally be possible. Until then, enthusiasm should be tempered with caution as we move forward into this new era of mechanical support.

Dr. Saunders is with the Division of Cardiothoracic Surgery, Maimonides Medical Center, Brooklyn, New York.

Screen cut latent TB rate among immigrants

BY MARY ANN MOON
Frontline Medical News

A new approach to screening has improved detection of tuberculosis in people applying to move to the United States, according to a report in Annals of Internal Medicine.

The previous preimmigration screening process involved chest radiography and, for those with abnormal radiographs, acid-fast bacilli smears of three consecutive sputum samples. If at least one smear was positive, the patient completed TB treatment overseas and was followed up after arrival in the United States. This approach failed, however, to detect some latent cases of TB that became reactivated soon after immigrants arrived in the United States.

The screening process also includes *Mycobacterium tuberculosis* culture results. For those who have at least one positive sputum smear or culture result, drug-susceptibility testing is done and directly observed therapy for TB is typically completed overseas before U.S. relocation is allowed, Yecai Liu, a mathematical statistician with the division of global migration and quarantine, Centers for Disease Control and Prevention, and his associates said.

To assess the effectiveness of the new screening algorithm, the researchers analyzed information in the CDC's disease notification database and the Department of Homeland Security's immigration records regarding 3,212,421 immigrants and refugees who were screened overseas and arrived in the United States during a 7-year period. A total of 51.4% were screened by the old method and 48.6% by the new method.

Before the new screen was implemented, the annual number of smear-negative TB cases among newly arrived immigrants and refugees was relatively constant, at approximately 1,500/year. That number dropped to 940 cases/year after the new screening method was implemented. The number of smear-negative but culture-positive TB cases diagnosed overseas among people bound for the United States increased from 4 to 629 cases per year, the researchers said (Ann. Intern. Med. 2015 March 17 [doi:10.7326/M14-2082]).

Expanding screening to cover exchange visitors and temporary workers from countries with a high incidence of TB might further reduce the disease rate in foreign-born populations, the researchers concluded.

VITALS

Key clinical point: A new screening program reduced tuberculosis cases among people immigrating to the United States.

Major finding: The mean annual number of latent TB cases among newly arrived immigrants and refugees went from 1,500 before the screening program to 940 after the program was implemented.

Data source: A cross-sectional analysis of TB cases among 3,212,421 immigrants and refugees.

Disclosures: This study was supported by the Centers for Disease Control and Prevention. Mr. Liu and his associates had no disclosures.

Meta-analysis: Oseltamivir shortens time to flu relief

BY SHARON WORCESTER
Frontline Medical News

Oseltamivir treatment in adults with influenza shortens the time to clinical symptom alleviation by about 1 day and substantially reduces the risk of lower respiratory tract complications and hospitalization, according to a meta-analysis of randomized, controlled trials involving 4,328 adults.

The findings of the study, which is the first to use individual patient data to evaluate the neuraminidase inhibitor, should put to rest persistent doubts about its efficacy and safety, said Dr. Arnold S. Monto of the University of Michigan School of Public Health, Ann Arbor, and his colleagues.

The intention-to-treat population of 1,591 patients with confirmed influenza had a significant 21% shorter time to clinical symptom alleviation, compared with the intention-to-treat

infected population of 1,302 patients who received placebo (97.5 hours vs. 122.7 hours; time ratio, 0.79).

The effects were somewhat attenuated in the 2,402 treated patients in the overall intention-to-treat population – with a 15% reduction in time to symptom alleviation – compared with the 1,926 placebo patients in that population. But the difference remained significant (median of 17.8 hours; time ratio, 0.85), the investigators said (Lancet 2015 Jan. 30 [doi:10.106/S0140-6736(14)62449-1]).

The risk of lower respiratory tract complications occurring more than 48 hours after randomization was 4.2% in oseltamivir-treated patients and 8.7% in those who received placebo, a 44% difference. The risk of hospitalization for any cause was 0.6% vs. 1.7%, a reduction of 63%.

The researchers included all published and unpublished Roche-sponsored randomized, placebo-controlled, double-blind trials of the standard prescribed oseltamivir dose of 75 mg twice daily in adults. Patients were within 36 hours of feeling unwell, had a fever and at least one respiratory and one constitutional symptom.

The Multiparty Group for Advice on Science funded the study via an unrestricted grant from Roche. Dr. Monto reported receiving fees from Roche outside of the submitted work.

Everolimus-eluting stents linked to higher MI risk

BY BIANCA NOGRADY
Frontline Medical News

Percutaneous coronary intervention with second-generation everolimus-eluting stents is associated with a similar risk of death but a higher risk of myocardial infarction and repeat revascularization than is coronary artery bypass grafting.

An observational registry study of 34,819 patients with multivessel coronary artery disease who underwent one or the other procedure showed a similar risk of death at a mean follow-up of 2.9 years between patients who underwent PCI with everolimus-eluting stents and those who underwent CABG (3.1% and 2.9% per year, hazard ratio, 1.04; $P = .50$).

However, those in the percutaneous coronary intervention group had a 51% greater risk of MI (95% confidence interval, 1.29-1.77; $P < .001$).

VITALS

Key clinical point: PCI with second-generation everolimus-eluting stents is associated with a similar risk of death but a higher risk of MI and repeat revascularization than does CABG.

Major finding: PCI was associated with a 51% greater risk of MI at 2.9 years of follow-up, compared with CABG.

Data source: An observational registry study of 34,819 patients with multivessel coronary artery disease.

Disclosures: The study was supported by Abbott Vascular. Dr. Bangalore has received consultant fees or honoraria from Abbott Vascular, Boehringer Ingelheim, Daiichi Sankyo, Gilead Sciences, Pfizer, and Unique Pharmaceuticals.

This increase in risk was significant only in patients who had incomplete revascularization and not in those with complete revascularization. Also, the increase in risk largely was tied to spontaneous MI.

"Trials comparing PCI with CABG have not been typically powered to evaluate differences in the rates of myocardial infarction, stroke, and death from any cause; instead, they have been

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observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients, particularly when budesonide is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of SYMBICORT should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of SYMBICORT with ketoconazole, and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) because adverse effects related to increased systemic exposure to budesonide may occur [see **DRUG INTERACTIONS** and **CLINICAL PHARMACOLOGY** in full Prescribing Information (12.3)].

Paradoxical Bronchospasm and Upper Airway Symptoms

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

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of SYMBICORT, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm.

Cardiovascular and Central Nervous System Effects

Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia [see **OVERDOSAGE**]. Therefore, SYMBICORT, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Formoterol, a component of SYMBICORT, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of formoterol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

Reduction in Bone Mineral Density

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

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5, or placebo on BMD was evaluated in a subset of 326 patients (females and males 41 to 88 years of age) with COPD in the 12-month study. BMD evaluations of the hip and lumbar spine regions were conducted at baseline and 52 weeks using dual energy x-ray absorptiometry (DEXA) scans. Mean changes in BMD from baseline to end of treatment were small (mean changes ranged from -0.01 - 0.01 g/cm^2). ANCOVA results for total spine and total hip BMD based on the end of treatment time point showed that all geometric LS Mean ratios for the pairwise treatment group comparisons were close to 1, indicating that overall, bone mineral density for total hip and total spine regions for the 12 month time point were stable over the entire treatment period.

Effect on Growth

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving SYMBICORT routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including SYMBICORT, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms [see **DOSAGE AND ADMINISTRATION** and **USE IN SPECIFIC POPULATIONS**].

Glaucoma and Cataracts

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with asthma and COPD following the long-term administration of inhaled corticosteroids, including budesonide, a component of SYMBICORT. Therefore, close monitoring is warranted in patients with a change in vision or with history of increased intraocular pressure, glaucoma, and/or cataracts.

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5, or placebo on development of cataracts or glaucoma were evaluated in a subset of 461 patients with COPD in the 12-month study. Ophthalmic examinations were conducted at baseline, 24 weeks, and 52 weeks. There were 26 subjects (6%) with an increase in posterior subcapsular score from baseline to maximum value (>0.7) during the randomized treatment period. Changes in posterior subcapsular scores of >0.7 from baseline to treatment maximum occurred in 11 patients (9.0%) in the SYMBICORT 160/4.5 group, 4 patients (3.8%) in the SYMBICORT 80/4.5 group, 5 patients (4.2%) in the formoterol group, and 6 patients (5.2%) in the placebo group.

Eosinophilic Conditions and Churg-Strauss Syndrome

In rare cases, patients on inhaled corticosteroids may present with systemic eosinophilic conditions. Some of these patients have clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of inhaled corticosteroids. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between budesonide and these underlying conditions has not been established.

Coexisting Conditions

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

Hypokalemia and Hyperglycemia

Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects [see **CLINICAL PHARMACOLOGY** in full Prescribing Information (12.2)]. The decrease in serum potassium is usually transient, not requiring supplementation. Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical studies with SYMBICORT at recommended doses.

ADVERSE REACTIONS

Long-acting beta$_2$-adrenergic agonists, such as formoterol one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Data from a large placebo-controlled US study that compared the safety of another long-acting beta$_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol [see **WARNINGS AND PRECAUTIONS**].

Systemic and inhaled corticosteroid use may result in the following:

- *Candida albicans* infection [see **WARNINGS AND PRECAUTIONS**]
- Pneumonia or lower respiratory tract infections in patients with COPD [see **WARNINGS AND PRECAUTIONS**]
- Immunosuppression [see **WARNINGS AND PRECAUTIONS**]
- Hypercorticism and adrenal suppression [see **WARNINGS AND PRECAUTIONS**]
- Growth effects in pediatric patients [see **WARNINGS AND PRECAUTIONS**]
- Glaucoma and cataracts [see **WARNINGS AND PRECAUTIONS**]

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.

Clinical Trials Experience in Asthma

Patients 12 years and older

The overall safety data in adults and adolescents are based upon 10 active- and placebo-controlled clinical trials in which 3393 patients ages 12 years and older (2052 females and 1341 males) with asthma of varying severity were treated with SYMBICORT 80/4.5 or 160/4.5 mcg taken two inhalations once or twice daily for 12 to 52 weeks. In these trials, the patients on SYMBICORT had a mean age of 38 years and were predominantly Caucasian (82%).

The incidence of common adverse events in Table 1 below is based upon pooled data from three 12-week, double-blind, placebo-controlled clinical studies in which 401 adult and adolescent patients (148 males and 253 females) age 12 years and older were treated with two inhalations of SYMBICORT 80/4.5 or SYMBICORT 160/4.5 twice daily. The SYMBICORT group was composed of mostly Caucasian (84%) patients with a mean age of 38 years, and a mean percent predicted FEV_1 at baseline of 76 and 68 for the 80/4.5 mcg and 160/4.5 mcg treatment groups, respectively. Control arms for comparison included two inhalations of budesonide HFA metered dose inhaler (MDI) 80 or 160 mcg, formoterol dry powder inhaler (DPI) 4.5 mcg, or placebo (MDI and DPI) twice daily. Table 1 includes all adverse events that occurred at an incidence of ≥3% in any one SYMBICORT group and more commonly than in the placebo group with twice-daily dosing. In considering these data, the increased average duration of patient exposure for SYMBICORT patients should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

Table 1 Adverse reactions occurring at an incidence of ≥3% and more commonly than placebo in the SYMBICORT groups: pooled data from three 12-week, double-blind, placebo-controlled clinical asthma trials in patients 12 years and older

Treatment*	SYMBICORT		Budesonide		Formoterol	Placebo
Adverse Event	80/4.5 mcg N = 277 %	160/4.5 mcg N =124 %	80 mcg N =121 %	160 mcg N = 109 %	4.5 mcg N = 237 %	N = 400 %
Nasopharyngitis	10.5	9.7	14.0	11.0	10.1	9.0
Headache	6.5	11.3	11.6	12.8	8.9	6.5
Upper respiratory tract infection	7.6	10.5	8.3	9.2	7.6	7.8
Pharyngolaryngeal pain	6.1	8.9	5.0	7.3	3.0	4.8
Sinusitis	5.8	4.8	5.8	2.8	6.3	4.8
Influenza	3.2	2.4	6.6	0.9	3.0	1.3
Back pain	3.2	1.6	2.5	5.5	2.1	0.8
Nasal congestion	2.5	3.2	2.5	3.7	1.3	1.0
Stomach discomfort	1.1	6.5	2.5	4.6	1.3	1.8
Vomiting	1.4	3.2	0.8	2.8	1.7	1.0
Oral Candidiasis	1.4	3.2	0	0	0	0.8
Average Duration of Exposure (days)	77.7	73.8	77.0	71.4	62.4	55.9

* All treatments were administered as two inhalations twice daily.

Long-term safety - asthma clinical trials in patients 12 years and older

Long-term safety studies in adolescent and adult patients 12 years of age and older, treated for up to 1 year at doses up to 1280/36 mcg/day (640/18 mcg twice daily), revealed neither clinically important changes in the incidence nor new types of adverse events emerging after longer periods of treatment. Similarly, no significant or unexpected patterns of abnormalities were observed for up to 1 year in safety measures including chemistry, hematology, ECG, Holter monitor, and HPA-axis assessments.

Clinical Trials Experience in Chronic Obstructive Pulmonary Disease

The incidence of common adverse events in Table 2 below is based upon pooled data from two double-blind, placebo-controlled clinical studies (6 and 12 months in duration) in which 771 adult COPD patients (496 males and 275 females) 40 years of age and older were treated with SYMBICORT 160/4.5, two inhalations twice daily. Of these patients 651 were treated for 6 months and 366 were treated for 12 months. The SYMBICORT group was composed of mostly Caucasian (93%) patients with a mean age of 63 years, and a mean percent predicted FEV_1 at baseline of 33%. Control arms for comparison included two inhalations of budesonide HFA (MDI) 160 mcg, formoterol (DPI) 4.5 mcg or placebo (MDI and DPI) twice daily. Table 2 includes all adverse events that occurred at an incidence of ≥3% in the SYMBICORT group and more commonly than in the placebo group. In considering these data, the increased average duration of patient exposure to SYMBICORT should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

Table 2 Adverse reactions occurring at an incidence of ≥3% and more commonly than placebo in the SYMBICORT group: pooled data from two double-blind, placebo-controlled clinical COPD trials

Treatment*	SYMBICORT	Budesonide	Formoterol	Placebo
Adverse Event	160/4.5 mcg N = 771 %	160 mcg N = 275 %	4.5 mcg N = 779 %	N = 781 %
Nasopharyngitis	7.3	3.3	5.8	4.9
Oral candidiasis	6.0	4.4	1.2	1.8
Bronchitis	5.4	4.7	4.5	3.5
Sinusitis	3.5	1.5	3.1	1.8
Upper respiratory tract infection viral	3.5	1.8	3.6	2.7
Average Duration of Exposure (days)	255.2	157.1	240.3	223.7

* All treatments were administered as two inhalations twice daily.

Lung infections other than pneumonia (mostly bronchitis) occurred in a greater percentage of subjects treated with SYMBICORT 160/4.5 compared with placebo (7.9% vs. 5.1%, respectively). There were no clinically important or unexpected patterns of abnormalities observed for up to 1 year in chemistry, haematology, ECG, ECG (Holter) monitoring, HPA-axis, bone mineral density and ophthalmology assessments.

Postmarketing Experience

The following adverse reactions have been reported during post-approval use of SYMBICORT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Some of these adverse reactions may also have been observed in clinical studies with SYMBICORT.

Cardiac disorders: angina pectoris, tachycardia, atrial and ventricular tachyarrhythmias, atrial fibrillation, extrasystoles, palpitations

Endocrine disorders: hypercorticism, growth velocity reduction in pediatric patients

Eye disorders: cataract, glaucoma, increased intraocular pressure

Gastrointestinal disorders: oropharyngeal candidiasis, nausea

Immune system disorders: immediate and delayed hypersensitivity reactions, such as anaphylactic reaction, angioedema, bronchospasm, urticaria, exanthema, dermatitis, pruritus

Metabolic and nutrition disorders: hyperglycemia, hypokalemia

Musculoskeletal, connective tissue, and bone disorders: muscle cramps

Nervous system disorders: tremor, dizziness

Psychiatric disorders: behavior disturbances, sleep disturbances, nervousness, agitation, depression, restlessness

Respiratory, thoracic, and mediastinal disorders: dysphonia, cough, throat irritation

Skin and subcutaneous tissue disorders: skin bruising

Vascular disorders: hypotension, hypertension

DRUG INTERACTIONS

In clinical studies, concurrent administration of SYMBICORT and other drugs, such as short-acting beta$_2$-agonists, intranasal corticosteroids, and antihistamines/decongestants has not resulted in an increased frequency of adverse reactions. No formal drug interaction studies have been performed with SYMBICORT.

Cardiovascular event rates similar in PCI and CABG

BY BIANCA NOGRADY
Frontline Medical News

Percutaneous coronary intervention with a sirolimus-eluting stent showed comparable rates of death, myocardial infarction and stroke to coronary artery bypass grafting in patients with coronary artery stenosis after 5 years in a randomized trial.

The PRECOMBAT (Premier of Randomized Comparison of Bypass-Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease) study randomized trial in 600 patients with unprotected left main coronary artery stenosis – 300 of whom were randomized to PCI and the rest to CABG – showed no significant difference in major adverse cardiac or cerebrovascular events (hazard ratio, 1.27; 95% confidence interval, 0.84-1.90; $P = 0.26$), according to a presentation at the American College of Cardiology meeting in San Diego.

However, the study did observe a twofold increase in the rate of ischemia-driven target vessel revascularization among patients treated with PCI, compared to those who underwent CABG (HR, 2.11; 95% CI, 1.16-3.84; $P = 0.012$).

The authors pointed out that this increase in revascularization did not appear to impact the study's harder endpoints.

"Given a higher rate of repeat revascularization even after the use of second-generation drug-eluting stents for unprotected left main coronary artery stenosis, frequent repeat revascularization could be an inherent weakness of stent-related treatments," wrote Dr. Jung-Min Ahn, from the Asan Medical Center, Seoul, and coauthors (J. Am. Coll. Cardiol. 2015; March 15 [doi:10.1016/j.jacc.2015.03.033]).

VITALS

Key clinical point: Percutaneous coronary intervention with sirolimus-eluting stents shows comparable rates of death, myocardial infarction, and stroke to coronary artery bypass grafting after 5 years.

Major finding: There were no significant differences in major adverse cardiac or cerebrovascular events between PCI and CABG in patients with unprotected left main coronary artery stenosis.

Data source: PRECOMBAT, a randomized trial in 600 patients with unprotected left main coronary artery stenosis.

Disclosures: The study was supported by the CardioVascular Research Foundation, Cordis, Johnson & Johnson, and the Korean Ministry of Health & Welfare. No conflicts of interest were disclosed.

PCI linked to higher rate of cardiovascular events

BY BIANCA NOGRADY
Frontline Medical News

SAN DIEGO – Percutaneous coronary intervention with everolimus-eluting stents is associated with significantly higher major adverse cardiovascular events than is coronary artery bypass grafting in patients with multivessel coronary artery disease, according to results of the BEST trial.

In the randomized noninferiority trial of 880 patients, there was a 47% higher rate of the primary endpoint of death, myocardial infarction, or target vessel revascularization among patients randomized to percutaneous coronary intervention with the new-generation drug-eluting stent than among those randomized to coronary artery bypass grafting, after a median of 4.6 years follow-up.

However, the differences in primary endpoint were not significant for noninferiority between the two groups at the 2-year follow-up mark, Dr. Seung-Jung Park said at the annual meeting of the American College of Cardiology.

The Xience everolimus-eluting stent used in BEST (Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients With Multivessel Coronary Artery Disease) is one of several bioabsorbable vascular scaffolds that have caught on in recent years. The working hypothesis behind the device is that by dissolving during a period of 12-24 months, the scaffold provides temporary bracing against restenosis but then disappears, allowing improved endovascular healing.

Patients were randomized after diagnostic coronary angiography to PCI (438 patients) or to CABG (442).

The study, which was terminated early because of slow enrollment, also found a significantly greater rate of the composite secondary endpoint of death, myocardial infarction, stroke, or repeat revascularization in the PCI group compared to the CABG group (19.9% vs. 13.3%, $P = .01$).

There were no significant differences between the two groups in the rate of the other secondary safety endpoint: a composite of death, MI, and stroke.

In total, 29 patients assigned to PCI died, compared with 22 assigned to CABG (6.6% vs. 5%, $P = .30$).

The rate of spontaneous myocardial infarction was significantly higher in the PCI group (4.3% vs. 1.6%, $P = .02$), as was the rate of repeat revascularization (11% vs. 5.4%, $P = .003$).

There were fewer incidences of major bleeding in the PCI group compared to the CABG group, although the rate of fatal major bleeding was similar for both arms of the study.

Diabetes status had a major negative impact on outcome for patients undergoing PCI, increasing the rate of the primary endpoint to 19.2%, compared to 9.1% in patients undergoing CABG ($P = .007$).

"In the BEST trial, PCI with everolimus-eluting stents was not shown to be noninferior to CABG with respect to the primary endpoint of death, myocardial infarction, or target vessel revascularization at 2 years," wrote Dr. Park of the University of Ulsan (South Korea) College of Medicine, and his coauthors.

The article was published online simultaneously with his presentation (N. Engl. J. Med. 2015 March 15 [doi:10.1056/NEJMoa1415447]).

"At longer-term follow-up (median 4.6 years), PCI was associated with a significant increase in the incidence of the primary endpoint, as compared to the incidence with CABG."

The authors suggested this difference was largely attributable to the higher rate of repeat target vessel revascularization in patients who had undergone PCI, as well as the spontaneous myocardial infarction and new lesion revascularization.

In contrast to previous studies, the researchers did not find a significant difference in the rate of stroke between the two groups.

"The reason for this discrepancy is not clear, but the use of off-pump CABG can avoid excessive manipulation of the aorta, and may have contributed to a reduced rate of stroke in the CABG group in our study," the authors noted.

The researchers acknowledged that the trial was not powered to detect differences in individual endpoints and that they did experience enrollment difficulties.

The CardioVascular Research Foundation, Abbott Vascular, and the Korea Healthcare Technology Research and Development Project supported the study. Dr. Park disclosed ties with Abbott, Cordis, Boston Scientific, and Medtronic, and has an ownership interest in the Cardiovascular Research Foundation.

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based on composite outcomes that include repeat revascularization," wrote Dr. Sripal Bangalore of New York University and coauthors.

Patients undergoing PCI with everolimus-eluting stents also had a greater than twofold increase in the risk of repeat revascularization (hazard ratio, 2.35; 95% CI, 2.14-2.58; $P < .001$), particularly in patients with three-vessel disease.

However, those in the PCI group also had a 58% lower risk of stroke than did those in the CABG group (95% CI, 0.50-0.76; $P < .001$), which was driven largely by a reduced risk in the first 30 days after the procedure (N. Engl. J. Med. 2015 March 16 [doi:10.1056/NEJMoa1412168]).

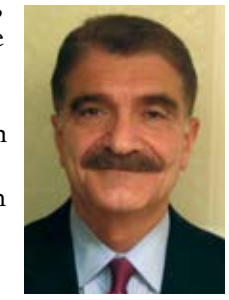
Within 30 days of the procedure, patients who underwent PCI showed lower risk of death and stroke but no significant differences in MI risk.

"Thus, the choice between CABG and PCI with everolimus-eluting stents may depend on whether complete revascularization can be achieved with PCI," the authors wrote. "If the answer is yes, the choice between PCI and CABG should be made on the basis of weighing the short-term risk of death and stroke against the long-term risk of revascularization with PCI."

The authors acknowledged the study was a nonrandomized, observational trial; it did not examine smoking and other comorbidities; and it did not capture neurologic events such as transient ischemic attack.

VIEW ON THE NEWS

PCI and CABG as complementary rather than competitive interventions



Dr. G. Hossein Almassi, FCCP, comments: These three studies presented at the American College of Cardiology meeting in San Diego compare PCI to CABG in patients with multivessel coronary artery disease. Both the randomized trial from Ulsan (South Korea) University (the BEST trial) and the observational study from New York used the newer generation everolimus-eluting stent. The primary endpoints of myocardial infarction and repeat revascularization were higher in the PCI group in both studies and, even more so in patients with diabetes in the BEST trial. The third study, the PRECOMBAT trial (Asan, Korea), was a randomized trial, comparing PCI using a sirolimus-eluting stent in patients with unprotected left main coronary disease. The outcomes at 5 years were similar to those of CABG, although the rate of ischemia-driven revascularization was twofold higher in the PCI group.

The Achilles heel of CABG in all the trials has been a higher rate of stroke at the initial hospitalization. Using a no touch aortic technique, the Ulsan group did not find a difference in the stroke rate between the PCI and the CABG groups.

CABG is a Class 1 indication for patients with left main stenosis, multivessel CAD and especially in those with left ventricular dysfunction and in diabetic patients (2011, ACCF/AHA guidelines). The seminal SYNTAX trial concluded that "CABG, as compared with PCI, is associated with a lower rate of major adverse cardiac or cerebrovascular events at 1 year among patients with three-vessel or left main coronary artery disease (or both) and should therefore remain the standard of care for such patients (N. Engl. J. Med. 2009;360:961-72).

SYNTAX also established the concept of a cardiac team including a cardiologist and a cardiac surgeon for the treatment of patients with CAD, a concept that is now being applied to patients undergoing percutaneous aortic valve implantation (TAVI or TAVR). This is now a Class 1 indication based on the 2011 ACCF/AHA CABG guidelines. Implementation of a cardiac team approach will lead to a paradigm shift in the treatment of CAD where PCI and CABG are implemented as complementary rather than competitive treatment modalities applied to patients with CAD as appropriate and based on patient's coronary anatomy (SYNTAX score) and clinical profile (STS score).

CRITICAL CARE COMMENTARY: Bed management – can we do better?

BY DR. MICHAEL J. WAXMAN, MBA, FCCP

Is it possible to give the best critical care while spending less money and resources doing it? Can we reduce waste while improving quality in a so-called lean approach to critical care? I believe that we have too many critical care beds, and we fill some of those beds with patients who can be taken care of at less intense levels of care—which are also less expensive.


DR. WAXMAN

Most work that is done to improve critical care looks at the quality of care. This is an area where a lot of data are accumulating. Take septic shock, for example. In the recently published ProCESS trial (The ProCESS Investigators. *N Engl J Med*. 2014. 370[18]:1683), the 60-day in-hospital mortality for septic shock was 18.2 to 21.0%. A lot of institutions (including mine) are struggling to get their septic shock mortality rate under 30%. Although some people critique the ProCESS trial mortality rate on patient selection, most of us try to figure out how to duplicate that lower rate. We do this in areas other than septic shock. If we are comparable in whatever quality statistic, we applaud our success. If we aren't comparable, we look at ways to improve, often based on what was done in that particular study.

How big of a financial burden is our critical care spending? According to an analysis of critical care beds by Halpern and colleagues (*Crit Care Med*. 2004;32[6]:1254), the number of hospital beds decreased 26.4% between 1985 and 2000, and the absolute number of critical care beds increased 26.2% (quantitated at 67,357 adult beds in 2007 per SCCM.org (www.sccm.org/Communications/Pages/CriticalCareStats.aspx). Critical care beds cost $2,674 per day in 2000, up from $1,185 (our CFOs tell us it is more like $3,500 to $4,000 per day now). They represented 13.3% of hospital costs, 4.2% of national health expenditures (NHE), and 0.56% of gross domestic product (GDP). There are 55,000 critically ill patients cared for each day in the United States, representing 5 million ICU patients per year. This is an enormous expenditure of money and it is growing.

Another interesting observation by Halpern and colleagues (*Crit Care Med*. 2004;32[6]:1254), was that critical care beds were only at 65% occupancy. This reflects my own experience where we operate at a 70% average ICU bed occupancy. We have created a larger financial burden with the fixed costs of one third more ICU beds than we actually use. Some bed availability is desirable., but how much is too much?

Are we doing the best job to give quality care and spend money wisely? Can we be more efficient in the throughput of patients and in their care? Admission criteria should be part of any unit, designed to place all patients who need ICU care appropriately in the ICU and exclude those whose care can be managed at a lesser level of intensity and cost. Discharge criteria, care protocols (eg, wake up and wean), checklists, and daily attention to the usual parameters (eg, DVT prophylaxis) are essential for high quality but efficient care. Done 24/7, we can maximize efficiency and quality with a minimum of ICU readmissions. Throughput is part of every physician's job description. The physician who wants one more day for his or her patient in the ICU simply because the nurse has fewer patients misses a number of points. Why would anyone want more exposure to resistant organisms, more noise, more awakenings, and less sleep, just to name a few? Keeping that non-ICU patient in the ICU bed might even delay the transfer of another patient coming from the ED, where we know they often don't get good ICU care.

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Are the beds filled only with what we intensivists would consider legitimate ICU patients, defined by both generally accepted (endotracheal tube in place) and individually specified criteria (unit specific related to other unit capabilities)? That would impact cost. An interesting article by Gooch and Kahn (*JAMA*. 2014; 311[6]:567) discussed the demand elasticity of the ICU. They considered the changes in case mix of patients between days of high and low bed availability. They contended that when ICU beds were available, there was an increase in patients who were unlikely to benefit from ICU admission. This group included a population of patients likely to survive and whose illness severity was low and a population of patients who were unlikely to survive and had a high illness severity. In other words, admissions expand to fill the staff-able beds. If this is true, it is another area where better management could lower costs without reducing the quality of care.

What if bed availability truly is reduced, often by a lack of critical care nursing staff if not physical beds? Here the answer is unclear. Town (*Crit Care Med*. 2014;42[9]:2037) looked at ICU readmission rates and

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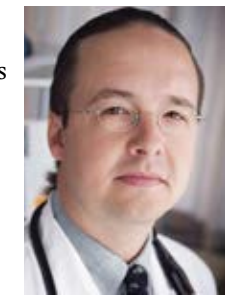
EDITOR'S COMMENTS

What is the ideal number of ICU beds for any given hospital? Which criteria should be used to determine who gets those beds? Who is the best gatekeeper to equitably allow admission to the ICU? And is there an app for that? The "right" answers to these questions vary depending on who is providing you with the answer key.



In the current *Critical Care Commentary*, Dr. Mike Waxman begins to unravel these complex issues and challenges us to do more with less. The data are clear that the ratio of ICU beds to general ward beds in US hospitals is markedly increased compared with other developed countries—and that we fill those beds with patients of lower acuity. Our epidemiology colleagues have made several other troubling observations of late: ICU admissions are growing fastest in patients aged 85 and older; most admissions from the ED are for symptoms—think chest pain or shortness of breath—that can signal a life-threatening condition but are more likely due to other problems, and the utilization of advanced imaging prior to ICU transfer has more than doubled in recent years. These findings suggest that factors such as changing demographics and medical-legal concerns are working against our "lean" approach to ICU care.

Equally troubling, many patients and non-ICU clinicians now view the hospital's general ward vs ICU bed designation on par with an airline gate agent's coach vs business class seat assignment. Through their eyes, patients receive more attention (2:1 nurse staffing and 24/7 in-house coverage anyone?) and more monitoring (Ah, I see you have the machine that goes "ping") behind the velvet ropes of the ICU. Lost from their view, buried deep in the bowels of the electronic medical record, is the fact that three times as many dollars are spent on their care without any incremental benefit. Sadly, many cost-conscious intensivists who attempt to use evidence-based criteria for ICU triage are steamrolled into submission by such misinformed clinicians and/or administrators under the misplaced auspices of patient safety. Hopefully, innovators such as Dr. Waxman will succeed in moving the needle and transform our JICU (just-in-case unit) beds back to ICU beds.

Dr. Lee E. Morrow, FCCP

Continued from previous page

the odds of having a cardiac arrest on the ward related to bed availability. Five ICUs with 63 beds total were examined. As ICU bed availability decreased, the odds of patients who were discharged from the ICU being readmitted to the ICU went up. Also, the odds of patients having a cardiac arrest on the ward increased when medical (not total) ICU beds were less available. In 2013, Wagner and colleagues (*Ann Intern Med*. 2013;159[7]:447) looked at 155 ICUs with 200,730 patients discharged from ICUs to hospital floors from 2001 to 2008. They examined what they call the strain metrics. These included the standardized ICU census, the proportion of new admissions, and the average predicted probability of death of the other patients in the ICU on the days of ICU discharge. When the strain metrics increased, ICU patients had shorter ICU length of stay and ICU readmission odds went up. They didn't, however, see an increased odds of death, a reduced odds of being discharged home, or a longer total hospital LOS. In a third study reported in 2008 in the Annals of Internal Medicine by Howell and colleagues (*Ann Intern Med*. 2008;149[11]:804), an innovative method of bed management was described. Because of an overcrowded ED and a high ambulance diversion rate, hospitalists implemented a system of bed control that was based on knowledge of ICU beds and ED congestion and flow. Bed assignments were better controlled by twice-daily ICU rounds and regular visits to the ED: throughput for admitted patients decreased by 98 min and time on diversion decreased significantly.

Mery and Kahn reported in 2013 (*Crit Care*. 2013;17[3]:315) that when ICU bed availability was reduced, there was a reduction in the likelihood of ICU admission within 2 h of a medical emergency team (MET) activation. What is interesting about this study done in three hospitals in Calgary, Alberta, Canada, is that there was an increased likelihood that the patient goals of care changed to comfort care when there was no bed availability compared with two ICU beds being available. Even more interesting is that hospital mortality did not vary significantly by ICU bed availability: more patients were moved to palliative care yet no more people died. Perhaps a lack of ICU beds expedited appropriateness of care.

To summarize, we have more patients in critical care beds where we spend ever-increasing amounts of our health-care dollars, but we seem to have more critical care beds than we need. We still have patients in our ICUs who would be better cared for elsewhere in our institutions. We can perform more cost-effective throughput when we are pressed to do so and usually we can do it safely.

I contend that the next improvement in lean ICU medicine will be better management tools. Comprehensive checklists help me where computer solutions have yet to be developed.

I am working to create hardware/software management solutions to make my job more cost-effective and to provide a sustainable process for what comes after me.

Dr. Waxman is Associate Professor of Medicine, KU School of Medicine, Kansas City, Kansas; Medical Director, Medical Surgical ICU/PCU, Research Medical Center; and Adjunct Professor, Rockhurst University, Helzberg School of Management, Kansas City, Missouri.

Fresh RBCs add no advantages for critically ill

BY BIANCA NOGRADY
Frontline Medical News

The use of fresh red blood cells for transfusion did not reduce mortality or improve other outcomes, compared with older red cells, based on a multicenter, blinded, randomized prospective study presented at the annual meeting of the International Society on Intensive Care and Emergency Medicine.

In the Age of Blood Evaluation (ABLE) study, researchers randomized 1,211 critically ill patients to red blood cells stored for less than 8 days and 1,219 patients to standard-issue cells stored for a mean of 22.4 days.

The study was conducted at 64 centers in Europe and Canada, where all blood units were leukoreduced and SAGM (saline-adenine-glucose-mannitol) suspended. Similar products are

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VITALS

Key clinical point: Fresh red blood cells didn't provide any additional gains in outcomes or reduce mortality at 90 days.

Major finding: The survival analysis of the time to death showed a hazard ratio of those in the fresh-blood group was 1.1, compared to those in the standard blood group (95% confidence interval, 0.9-1.2) ($P = .38$).

Data source: A multicenter, blinded, randomized prospective study in 2,430 patients receiving red blood cell transfusions.

Disclosures: The study was supported by the Canadian Institutes of Health Research, Fonds de Recherche du Québec–Santé, the National Institute for Health Research Evaluation, the French Ministry of Health, and the Etablissement Français du Sang, and Sanquin Blood Supply. Two authors reported grants and personal fees from pharmaceutical companies outside the submitted work, while others reported financial support from the study funding sources.

Continued from page 24

supplied in the United States, but red cells are suspended in additive solution 3 (AS3) rather than SAGM.

At 90 days, 37% of patients in the fresh-blood group and 35% of patients in the standard blood group had died. The survival analysis of the time to death showed a hazard ratio of those in the fresh-blood group was 1.1, compared with those in the standard blood group (95% confidence interval, 0.9-1.2; $P = .38$). There were no differences in death rate, organ failure, acute respiratory distress, cardiac complications, thrombosis, infection, or acute transfusion reaction.

There were no differences in length of hospital stay or duration of supportive care such as mechanical ventilation.

"Although [other] initial studies showed an association between longer red-cell storage and adverse outcomes, these associations may have been spurious owing to sicker patients receiving more units with longer storage, the overlap between comparison groups in the age of the red cells transfused, and the inclusion of transfusions that occurred after the clinical events," Dr. Jacque Lacroix of University of Montreal and his coauthors wrote in the March 17 edition of the New England Journal of Medicine (doi:10.1056/NEJMoa1500704).

FDA approves filgrastim as first 'biosimilar' in US

BY ELIZABETH MECHCATIE
Frontline Medical News

A biosimilar version of filgrastim, the leukocyte growth factor marketed as Neupogen, has been approved by the Food and Drug Administration, the first approval of a biosimilar in the United States.

The filgrastim biosimilar will be marketed as Zarxio by Sandoz and is approved for the same indications as Amgen's Neupogen, which was licensed by the FDA in 1991. There are at least four other biosimilar versions of biologic products being reviewed by the FDA, including an infliximab (Remicade) biosimilar. Biosimilars are expected to make biological therapies available at a lower price, the FDA said.

The nonproprietary name for Zarxio is "filgrastim-sndz."

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Trauma patients need more enoxaparin to halt VTEs

BY M. ALEXANDER OTTO
Frontline Medical News

PHOENIX – Trauma patients probably need an elevated dose of enoxaparin – perhaps 40 mg twice daily – to prevent venous thromboembolisms, according to a prospective study of 85 trauma patients at the Palmetto Health Richland Hospital in Columbia, S.C.

Also, antifactor 10a – a blood test often used in research to gauge how well enoxaparin (Lovenox) is thinning the blood – doesn't work very well as an empiric measure of anticoagulation; thromboelastography may be better, lead investigator Janise Phillips, Pharm.D., said at the Critical Care Congress, sponsored by the Society of Critical Care Medicine.

Her team tracked trauma patients who had at least three consecutive doses of enoxaparin prophylaxis for venous thromboembolism and at least one peak antifactor 10a level drawn; enoxaparin doses were adjusted as needed to hit a weekly antifactor 10a level of 0.20-0.40 IU/mL, which is thought to be the therapeutic range for enoxaparin.

Critically ill trauma patients – and perhaps burn patients – need higher anticoagulant doses.

DR. PHILLIPS

Patients were in the ICU for a median of about 10 days, and in the hospital for about 2-3 weeks.

The types of trauma were not reported in the study, but the investigation confirms prior findings that critically ill trauma patients – and perhaps burn patients – need higher anticoagulant doses.

Overall, 65% of patients (13) on an initial enoxaparin regimen of 30 mg subcutaneously twice daily were below anti–factor 10a levels of 0.20-0.40 IU/mL after their first dose; 22% (8) were at a subtherapeutic level after an initial dose of 40 mg once daily; and 21% (6) were at a subtherapeutic level after an initial dose of 40 mg twice daily.

Anti–factor 10a levels didn't match well with clinical benefit. VTEs were diagnosed in 15% of patients (4) with an initial subtherapeutic anti–factor 10a level, but 15% (4) bled on their subtherapeutic dose; 8.5% of patients (4) with an initial therapeutic level had a VTE, vs. none who were supratherapeutic after their initial dose. However, 9% of supratherapeutic patients (1) had an enoxaparin bleed.

"These were trauma patients in and out of surgery. A lot of the time, we had to stop the dose and hold it, which may" explain why subtherapeutic patients had the highest VTE risk, said Dr. Phillips, now a critical care pharmacist at the Cleveland Clinic hospital in Abu Dhabi, United Arab Emirates.

The fact that both VTEs and bleeding were most likely in underdosed patients could mean that anti–factor 10a "is really not the best marker for VTE risk," Dr. Phillips said.

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FDA approves Anthrasil to treat inhalational anthrax

BY DEEPAK CHITNIS
Frontline Medical News

The Food and Drug Administration has approved Anthrasil, Anthrax Immune Globulin Intravenous (Human), for the treatment of inhalational anthrax when used with appropriate antibacterial drugs.

Dr. Karen Midthun, director of the Center for Biologics Evaluation and Research, said in a statement that Anthrasil "will be stored in U.S. Strategic National Stockpile to facilitate its availability in response to an anthrax emergency."

FDA NEWS

Anthrasil was purchased by the Department of Health & Human Services' Biomedical Advanced Research and Development Authority (BARDA) in 2011, but because it was not approved, its use prior to FDA approval would have required an emergency use authorization from the FDA.

The efficacy of Anthrasil was studied in animals, the FDA said. The survival rate for monkeys exposed to *Bacillus anthracis* spores and then given Anthrasil was between 36% and 70%. None of the monkeys given placebo survived. Rabbits had a 26% survival rate when given the drug, compared with 2% of those given placebo. Safety was tested in 74 healthy human volunteers; the most commonly reported side effects included headache, back pain, and nausea.

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Environmental factors could increase U.S. anthrax cases

BY DEEPAK CHITNIS
Frontline Medical News

WASHINGTON – Isolated cases of anthrax in Minnesota and elsewhere, along with the disease's relative ease of transmission from animals or plants to humans, should heighten U.S. physicians' awareness of anthrax's symptoms and treatments, according to Dr. Jason K. Blackburn.

"[Anthrax] is something that our international partners deal with on an annual basis [as] we can see the disease reemerging, or at least increasing, in annual reports on humans in a number of countries," said Dr. Blackburn of the University of Florida in Gainesville, at a meeting on biodefense and emerging diseases sponsored by the American Society for Microbiology.

"Here in the United States, we're seeing it shift from a livestock disease [to] a wildlife disease, where we have these populations that we can't reach with vaccines, and where surveillance is very logistically challenging," he said.

Environmental factors can drive higher incidences of anthrax cases. Temperature, precipitation, and vegetation indices are key variables that facilitate anthrax transmission and spread of the disease. Geographically, lowland areas also have higher prevalences of the disease.

Dr. Blackburn and his colleagues used predictive models to quantify the theory that anthrax case rates increase during years that have wet springs followed by hot, dry summers in the region of Western Texas. Using these data would allow scientists and health care providers to predict which years would have an increased risk for anthrax cases in humans, Dr. Blackburn said, and could help hospitals and clinics effectively prepare to treat a higher influx of these cases and prevent possible outbreaks.

Although relatively large numbers of human anthrax cases persist in parts of the world, cases in the United States have been mostly relegated to livestock.

However, during the last decade, there has been a noticeable shift in cases from livestock to wildlife. The newfound prevalence in wildlife species, along with the continued presence in domestic animals such as cattle and sheep, mean that transmission to humans could become even easier.

"Human cases are usually driven by direct human interaction with mammalian hosts," said Dr. Blackburn. Dr. Blackburn did not report any disclosures.

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Lung cancer screening criteria may need changes

BY NICOLA GARRETT
Frontline Medical News

Fewer patients diagnosed with lung cancer are meeting the U.S. Preventive Services Task Force criteria for screening with low-dose computed tomography.

Screening criteria may need to be changed, since fewer American adults now have a smoking history of 30 pack-years and have quit within the last 15 years, according to Dr. Ping Yang of the division of epidemiology at the Mayo Clinic, Rochester, Minn., and her colleagues.

A retrospective analysis of patients with pathologically confirmed lung cancer in Olmsted County, Minn., between 1984 and 2011 found that, in 1984-1990, 57% of patients with diagnosed lung cancer met USPSTF screening guidelines. By 2005-2011, the figure had dropped significantly to 43%.

The proportion of women who would have been eligible under the criteria decreased from 52% to 37% in the same time period; the proportion of men had dropped from 60% to 50%, they found.

"More sensitive screening criteria may need to be identified while balancing the potential harm from computed tomography," Dr. Yang and her colleagues wrote (JAMA 2015; 313:853-5).

Lung cancer incidence trends in this study were comparable with Surveillance, Epidemiology, and End Results data, but may not be generalizable to the U.S. population, they added.

The study was funded by the National Institutes of Health and the Mayo Clinic Foundation. The authors reported no relevant conflicts of interest.

VIEW ON THE NEWS

Dr. Jennifer D. Cox, FCCP, comments: Since 2005, a significant proportion of patients who are diagnosed with lung cancer were ineligible for low-dose CT screening for lung cancer under the current guidelines. This was most prevalent in the female population. The changing demographics of tobacco use in this country may be in part to blame. The proportion of patients currently smoking with a 30-plus-year smoking history or having quit within the last 15 years is declining. The current criteria are excluding a significant number of patients who are eventually diagnosed with lung cancer. Maybe it's time to revisit the current guidelines – determine what variables are unique to this group of patients, evaluate those variables for increasing sensitivity of the screening guidelines, and update our current practice. For a screening program to work, we need to find more patients early, not less, while limiting the potential for harm from radiation exposure.

Periop atrial natriuretic peptide linked to lower recurrence

BY JENNIFER KELLY SHEPPHIRD
Frontline Medical News

Patients with lung cancer who underwent surgery to remove solid tumors and who were treated with atrial natriuretic peptide had significantly lower cancer recurrence than did untreated patients, a study showed.

Investigators retrospectively evaluated patients with lung cancer who underwent surgical removal of tumors; 77 patients received perioperative treatment with atrial natriuretic peptide (ANP), and 390 patients did not receive ANP treatment.

ANP-treated patients had significantly greater 2-year relapse-free survival (RFS) after surgery than did those who did not receive ANP (91% vs. 75%, $P = .018$).

An analysis of propensity-matched patients also showed significantly greater 2-year RFS in the ANP group (91% vs. 67%, $P = .0013$), reported Dr. Takashi Nojiri of Osaka (Japan) University, and associates.

"We demonstrated that cancer recurrence after curative surgery was significantly lower in ANP-treated patients than in control patients, suggesting that ANP could potentially be used to prevent cancer recurrence after surgery," wrote Dr. Nojiri and colleagues (Proc. Natl. Acad. Sci. USA 2015 March 16 [doi:10.1073/pnas.1417273112]).

VIEW ON THE NEWS

Dr. Jennifer D. Cox, FCCP, comments: The same authors have previously published data in patients with elevated preoperative brain natriuretic peptide levels showing a decrease in cardiopulmonary complications after lung cancer surgery with perioperative atrial natriuretic peptide infusions. Looking retrospectively at the same group of patients, they found a significant 2-year relapse-free survival in those patients who received the ANP infusions versus those who did not (91% vs. 75%). Physiologically, ANP decreases the inflammatory response of the vascular endothelium to surgical stress. The decreased ability of tumor cells to adhere to the vascular endothelial cells decreases the chance of future metastasis. A large randomized multicenter trial should be undertaken before adopting this into practice, but the results are encouraging.

Nivolumab approved for advanced squamous NSCLC

BY LAURA NIKOLAIDES
Frontline Medical News

The Food and Drug Administration has expanded approval of the PD-1 inhibitor nivolumab to include treatment of patients who have metastatic squamous non–small cell lung cancer and progress following platinum-based chemotherapy.

The FDA approved nivolumab to treat patients who have metastatic melanoma and no longer respond to other drugs. Nivolumab for squamous non–small cell lung cancer (NSCLC) was reviewed under the FDA's priority review program, and was approved more than 3 months ahead of schedule, the FDA said.

Efficacy was established in a trial of 272 patients with metastatic squamous NSCLC; the median overall survival was increased by 3.2 months in 135 patients who received nivolumab, compared with 137 on docetaxel.

The safety and efficacy of nivolumab to treat squamous NSCLC was also supported by a single-arm trial of 117 participants who had progressed after receiving a platinum-based therapy and at least one additional systemic regimen. The objective response rate was 15%.

The most common side effects of nivolumab are fatigue, shortness of breath, musculoskeletal pain, decreased appetite, cough, nausea, and constipation. The most serious side effects are severe immune-mediated side effects involving healthy organs, including the lung, colon, liver, kidneys, and hormone-producing glands. The drug is marketed as Opdivo by Bristol-Myers Squibb.

VIEW ON THE NEWS

Dr. Jennifer D. Cox, FCCP, comments: New therapies for the treatment of advanced lung cancer are desperately needed. Nivolumab was recently approved for treatment of advanced lung cancer in patients that progressed on standard therapy. The early approval was done based on a 3.2-month survival over docetaxel. The common side effects would appear to be more inconvenient than detrimental. However, having seen and taken care of the patients with the severe immune-mediated side effects, I can say nivolumab is not a benign drug. My take on a medication that has any survival advantage will always be, 'Is the quality of life for the patient during those 3 months good or is it poor?' Survival is more than just the number of days a patient is alive, and I would like that kind of information provided as well.

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What if your PAH patient may not have PAH?

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

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

1 in 25*

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

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

VISIT **scan4CTEPH.COM** FOR MORE INFORMATION

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Screening for CTEPH in Patients With Suspected Pulmonary Hypertension

presented by

RICHARD CHANNICK, MD

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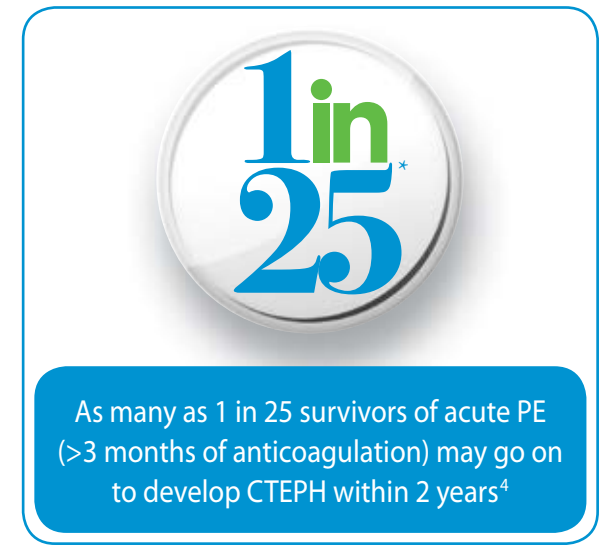

CTEPH IS A FORM OF PULMONARY HYPERTENSION

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

1: Pulmonary arterial hypertension

2: PH due to left heart disease

3: PH due to lung diseases and/or hypoxia

4: CTEPH

5: PH with unclear multifactorial mechanisms

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

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

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

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

HOW DOES CTEPH DEVELOP?

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

HOW COMMON IS CTEPH?

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

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

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

HOW DO WE SCREEN FOR CTEPH?

As noted, symptoms of CTEPH are nonspecific, and as a result, CTEPH is often misdiagnosed and is under recognized in practice.[6] If after at least 3 months of anticoagulation following an episode of acute PE a patient still has or develops symptoms of dyspnea, fatigue, decreased exercise capacity, or another of the symptoms of PH, one should suspect and either screen for CTEPH or refer the patient to a PH specialist who can perform CTEPH screening.[18,19]

As noted above, as many as 30% of patients who are ultimately diagnosed with CTEPH may have no history of overt acute PE, so any patient who has unexplained dyspnea should also be screened for CTEPH.[9, 16,17]

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

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

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

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

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

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

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

CONFIRMATION OF CTEPH DIAGNOSIS

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

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

CTEPH TREATMENT IN SURGICAL CANDIDATES: PULMONARY THROMBOENDARTERECTOMY

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

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

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PP-400-US-1575 March 2015

ICD-10 cometh

BY DR. MICHAEL E. NELSON, FCCP

Just when you thought the flu season was over. … The ICD-10 version!

For our second set of codes we have chosen influenza as this is a diagnosis fresh on the mind of most physicians at this time. This set of codes is quite complex and also contains "placeholders." According to the ICD-10-CM Official Guidelines for Coding and Reporting available at www.cms.gov/Medicare/Coding/ICD10/2015-ICD-10-CM-and-GEMs.html,

The ICD-10-CM utilizes a placeholder character "X." The X is used as a placeholder at certain codes to allow for future expansion.

Where a placeholder exists, the X must be used in order for the code to be considered a valid code. The ICD-10 CM codes for influenza are listed below.

Influenza and pneumonia (J09-J18)

Excludes 2:
- allergic or eosinophilic pneumonia (J82)
- aspiration pneumonia NOS (J69.0)
- meconium pneumonia (P24.01)
- neonatal aspiration pneumonia (P24.-)
- pneumonia due to solids and liquids (J69.-)
- congenital pneumonia (P23.9)
- lipid pneumonia (J69.1)
- rheumatic pneumonia (I00)
- ventilator associated pneumonia (J95.851)

J09 Influenza due to identified novel influenza A virus with pneumonia

Excludes 1:
- influenza due to other identified influenza virus (J10.-)
- influenza due to unidentified influenza virus (J11.-)
- seasonal influenza due to other identified influenza virus (J10.-)
- seasonal influenza due to unidentified influenza virus (J11.-)

J09.X1 Inclusion Terms:
- Avian influenza
- Bird influenza
- Influenza A/H5N1
- Influenza of other animal origin, not bird or swine
- Swine influenza virus (viruses that normally cause infections in pigs)

J09.X1 Influenza due to identified novel influenza A virus with pneumonia

Code Also: , if applicable, for associated:
- lung abscess (J85.1)
- other specified type of pneumonia

J09.X2 Influenza due to identified novel influenza A virus with other respiratory manifestations

Inclusion Terms:
- Influenza due to identified novel influenza A virus NOS
- Influenza due to identified novel influenza A virus with laryngitis
- Influenza due to identified novel influenza A virus with pharyngitis
- Influenza due to identified novel influenza A virus with upper respiratory symptoms

Use Additional: code, if applicable, for associated:
- pleural effusion (J91.8)
- sinusitis (J01.-)

J09.X3 Influenza due to identified novel influenza A virus with gastrointestinal manifestations

Inclusion Terms:
- Influenza due to identified novel influenza A virus gastroenteritis

Excludes 1:
- 'intestinal flu' [viral gastroenteritis] (A08.-)

J09.X9 Influenza due to identified novel influenza A virus with other manifestations

Inclusion Terms:
- Influenza due to identified novel influenza A virus with encephalopathy
- Influenza due to identified novel influenza A virus with myocarditis
- Influenza due to identified novel influenza A virus with otitis media

Use Additional:
- code to identify manifestation

J10 Influenza due to other identified influenza virus

Excludes 1:
- influenza due to avian influenza virus (J09.X-)
- influenza due to swine flu (J09.X-)
- influenza due to unidentified influenza virus (J11.-)

J10.0 Code Also: associated lung abscess, if applicable (J85.1)

J10.00 Influenza due to other identified influenza virus with unspecified type of pneumonia

J10.01 Influenza due to other identified influenza virus with the same other identified influenza virus pneumonia

J10.08 Influenza due to other identified influenza virus with other specified pneumonia

J10.1 Influenza due to other identified influenza virus with other respiratory manifestations

Inclusion Terms:
- Influenza due to other identified influenza virus NOS
- Influenza due to other identified influenza virus with laryngitis
- Influenza due to other identified influenza virus with pharyngitis
- Influenza due to other identified influenza virus with upper respiratory symptoms

Use Additional:
- code for associated pleural effusion, if applicable (J91.8)
- code for associated sinusitis, if applicable (J01.-)

J10.2 Influenza due to other identified influenza virus with gastrointestinal manifestations

Inclusion Terms:
- Influenza due to other identified influenza virus gastroenteritis

Excludes 1:
- intestinal flu' [viral gastroenteritis] (A08.-)

J10.8 Influenza due to other identified influenza virus with other manifestations

J10.81 Influenza due to other identified influenza virus with encephalopathy

J10.82 Influenza due to other identified influenza virus with myocarditis

J10.83 Influenza due to other identified influenza virus with otitis

Use Additional: code for any associated perforated tympanic membrane (H72.-)

J10.89 Influenza due to other identified influenza virus with other manifestations

Use Additional:
- codes to identify the manifestations

J11 Influenza due to unidentified influenza virus

J11.0 Influenza due to unidentified influenza virus with

Code Also: associated lung abscess, if applicable (J85.1)

J11.00 Influenza due to unidentified influenza virus with unspecified type of pneumonia

Inclusion Terms:
- Influenza with pneumonia NOS

J11.08 Influenza due to unidentified influenza virus with specified pneumonia

Code Also: other specified type of pneumonia

J11.1 Influenza due to unidentified influenza virus with other respiratory manifestations

Inclusion Terms:
- Influenza NOS
- Influenza laryngitis NOS
- Influenza pharyngitis NOS
- Influenza with upper respiratory symptoms NOS

Use Additional:
- code for associated pleural effusion, if applicable (J91.8)
- code for associated sinusitis, if applicable (J01.-)

J11.2 Influenza due to unidentified influenza virus with gastrointestinal manifestations

Inclusion Terms:
- Influenza gastroenteritis NOS

Excludes 1:
- 'intestinal flu' [viral gastroenteritis] (A08.-)

J11.8 Influenza due to unidentified influenza virus with other manifestations

J11.81 Influenza due to unidentified influenza virus with encephalopathy

Inclusion Terms:
- Influenza encephalopathy NOS

J11.82 Influenza due to unidentified influenza virus with myocarditis

Inclusion Terms:
- Influenza myocarditis NOS

J11.83 Influenza due to unidentified influenza virus with otitis media

Inclusion Terms:
- Influenza otitis media NOS

Use Additional:
- code for any associated perforated tympanic membrane (H72.-)

J11.89 Influenza due to unidentified influenza virus with other manifestations

Use Additional:
- codes to identify the manifestations

J12 Viral pneumonia, not elsewhere classified

Code First:
- associated influenza, if applicable (J09.X1, J10.0-, J11.0-)

Code Also:
- associated abscess, if applicable (J85.1)

Includes:
- bronchopneumonia due to viruses other than influenza viruses
- aspiration pneumonia due to anesthesia during labor and delivery (O74.0)

Excludes 1:
- aspiration pneumonia due to anesthesia during pregnancy (O29)
- aspiration pneumonia due to anesthesia during puerperium (O89.0)
- aspiration pneumonia due to solids and liquids (J69.-)
- aspiration pneumonia NOS (J69.0)
- congenital pneumonia (P23.0)
- congenital rubella pneumonitis (P35.0)
- interstitial pneumonia NOS (J84.9)
- lipid pneumonia (J69.1)
- neonatal aspiration pneumonia (P24.-)

J12.0 Adenoviral pneumonia

J12.1 Respiratory syncytial virus pneumonia

J12.2 Parainfluenza virus pneumonia

J12.3 Human metapneumovirus pneumonia

J12.8 Other viral pneumonia

12.81 Pneumonia due to SARS-associated coronavirus

Inclusion Terms:
- Severe acute respiratory syndrome NOS

12.89 Other viral pneumonia

12.9 Viral pneumonia, unspecified

California physicians sue state over suicide law

BY ALICIA GALLEGOS
Frontline Medical News

A group of physicians and patients are suing the state of California over a law that they say exposes doctors to criminal prosecution for providing terminally ill patients aid in dying.

Three doctors and three cancer patients – two of whom are also doctors – filed suit against the state, calling on California to clarify a portion of its assisted-suicide statute. The law makes it a felony to deliberately help a person commit suicide.

In their suit, the plaintiffs claim physicians who write prescriptions for mentally competent, terminally ill patients should not face legal penalties. The choice for a peaceful death by a dying patient is not suicide, nor is a physician assisting such a patient in "committing suicide," the complaint argues. In addition, the physicians assert that patients facing the end of their lives have a right under the California state Constitution to make autonomous decisions about their bodies and how they will die.

In a statement, plaintiff Dr. Robert Brody, professor of medicine at the University of California, San Francisco, said competent, terminally ill adults have the right to a peaceful death in a controlled and clinically sound way.

"The current murky legal landscape means that physicians are placed at risk and must choose between potentially skirting the law to respect their patients' choices or abandoning them to bad information, uncertainty, or violence," he said in the statement.

The lawsuit comes after the high-profile death of terminally ill patient Brittany Maynard, who moved from California to Oregon to take advantage of that state's Death With Dignity law.

The Disability Rights Legal Center, which is representing the plaintiffs in the California case, also recently filed suit in New York over the same issue. In that case, several physicians and patients are asking New York judges to clarify the ability of mentally competent, terminally ill New York patients to obtain aid in dying from their physician.

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Watchman device alternative to warfarin in AF

BY ELIZABETH MECHCATIE
Frontline Medical News

The Watchman left atrial appendage closure device has been approved in the United States as an alternative to warfarin for patients with nonvalvular atrial fibrillation, for a narrower indication than the one submitted for approval to the Food and Drug Administration.

The device is a percutaneously delivered permanent cardiac implant placed in the left atrial appendage (LAA) to prevent the embolization of thrombi formed there, and is manufactured by Boston Scientific. The FDA approved the Watchman for reducing the risk of thromboembolism from the LAA in patients with nonvalvular atrial fibrillation "who are at increased risk for stroke and systemic embolism based on $CHADS_2$ or CHA_2DS_2-VASc scores; are deemed by their physicians

to be suitable for warfarin; and have an appropriate rationale to seek a nonpharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device, compared to warfarin," according to a statement issued by the company.

The approved indication is worded differently from the proposed indication submitted to the FDA for approval and discussed at an FDA panel meeting, to "prevent thromboembolism from the left atrial appendage." The changes include the replacement of "prevent" with "reduce the risk" of thromboembolism, and the addition of the following qualifiers: In patients who "are deemed by their physicians to be suitable for warfarin," and who have "an appropriate rationale to seek a nonpharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin."

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At a meeting of the FDA's Circulatory System Devices Panel, the panel voted 6-5 with 1 abstention that the benefits of the device outweighed its risks for the proposed indication.

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Long-term DAPT offers ongoing post-MI benefit

BY MITCHEL L. ZOLER
Frontline Medical News

SAN DIEGO – The idea that patients with established coronary disease can derive important, secondary-prevention benefit from prolonged dual-antiplatelet therapy received a major boost with the results of a major, international controlled trial with more than 21,000 patients.

Results from the PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54) showed putting post–myocardial infarction patients on dual-antiplatelet therapy (DAPT) with aspirin and the thienopyridine ticagrelor (Brilinta) for a median of 33 months cut the combined incidence of cardiovascular death, MI, or stroke by a relative 15%, compared with patients on aspirin alone as well as the other standard treatments used for post-MI patients, Dr. Marc S. Sabatine reported at the annual meeting of the American College of Cardiology.

The findings added to the growing body of evidence that long-term – and possibly lifelong – DAPT is a key part of secondary prevention. Last year, results from the DAPT (Dual Antiplatelet Therapy) trial (N. Engl. J. Med. 2014;371:2155-66) supplied evi-

Dr. Robert Harrington: Assessing a patient's bleeding risk is important.

dence for this in acute coronary syndrome patients who had undergone percutaneous coronary intervention. The PEGASUS-TIMI 54 trial did not require that enrolled post-MI patients had undergone PCI, but the reality is that this is the way most MI patients get managed, and in PEGASUS-TIMI 54 roughly 83% of the patients had a PCI history.

The new findings also highlighted the risk-benefit trade-off that DAPT means for patients. In PEGASUS-TIMI 54 the increased incidence of major bleeding events roughly matched the decreased rate of major cardiovascular events prevented. But while the incidence of bleeds categorized as TIMI major bleeds more than doubled in the patients randomized to DAPT, compared with those on aspirin only, the prolonged treatment with ticagrelor did not result in an increase in fatal bleeds or in intracranial hemorrhages, the two most feared types of TIMI major bleeds.

"I'd much rather prevent cardiovascular deaths, MIs, and strokes even at the expense of causing reversible, nonfatal bleeding events," said Dr. Sabatine, professor of medicine at Har-

Continued on following page

Continued from previous page

vard Medical School in Boston and chairman of the TIMI Study Group at Brigham and Women's Hospital.

Another notable adverse effect from ticagrelor treatment was a roughly threefold increased incidence of dyspnea, which led to drug discontinuation in 5%-7% of patients, depending on whether they received ticagrelor at 60 mg b.i.d. or 90 mg b.i.d. The study results showed a reduced rate of both bleeding and dyspnea in patients randomized to receive the 60-mg b.i.d. dosage, compared with those who received the 90-mg b.i.d. dosage, which is the standard ticagrelor dosage and the formulation now sold.

At the same time, the efficacy of the 60-mg b.i.d. dosage for preventing ischemic events equaled that of the higher dosage. But as of today, it is impossible for a physician to prescribe a 60-mg formulation of ticagrelor because the manufacturer does not sell it.

Several cardiologists from PEGASUS-TIMI 54 at the meeting said that they agreed with Dr. Sabatine and felt that the benefits from prolonged DAPT with ticagrelor outweighed the downside of an increased bleeding risk.

"I think that the benefit is greater than the risk. None of us wants to see patients experience bleeding, but I was encouraged that fatal bleeds and intracranial hemorrhages were no different," commented Dr. Elliott M. Antman, professor of medicine at Harvard.

"The benefits outweigh the bleeding risk, but I wouldn't trivialize the bleeding risk. Assessing a patient's bleeding risk is really important," commented Dr. Robert Harrington, professor of medicine at Stanford (Calif.) University.

But others at the meeting said that the elevated bleeding risk gave them pause. "There clearly is a price to be paid even if extended-duration DAPT reduces MI and stent thrombosis. I believe only the highest-risk patients – those with acute coronary syndrome and ST-elevation MI – are the ones for whom I'd even consider it. Unless we can reduce bleeding risk, maybe with even lower doses [of ticagrelor], stopping aspirin, or using a reversal agent, we will be causing bleeds that are very relevant to patients," commented Dr. Ajay J. Kirtane, an interventional cardiologist at Columbia University in New York.

Dr. Kirtane also questioned whether TIMI major bleeding was the appropriate measure of bleeding risk in the context of a study like PEGASUS-TIMI 54. "Historically, TIMI major bleeding was derived from studies of acute heart attack patients getting fibrinolytic therapy.

"That is a very different population from this one. In my mind, the combination of TIMI major and minor bleeding would be more encompassing, and for patients the bleeding risks of these therapies are real and have been associated with bad sequelae," he said in an interview.

Dr. Elliott M. Antman: I think the benefit is greater than the risk.

When placed in the context of prior reports, the new findings also raise the possibility that the generic, and hence much cheaper, thienopyridine clopidogrel might provide roughly the same long-term benefit as the more expensive ticagrelor, especially for patients without a genetic profile that makes them poor clopidogrel metabolizers. This may be an attractive option for patients who have a problem paying for ticagrelor long term. "I'd rather prescribe a patient a cheaper medication that might be a bit less effective than create an economic hardship," Dr. Harrington said in an interview. The results from the DAPT trial, which included some post-PCI patients who received long-term DAPT with clopidogrel plus aspirin, "give you a certain comfort" with the idea of substituting clopidogrel for ticagrelor when affordability is a major concern, Dr. Harrington noted.

Dr. Marc S. Sabatine: DAPT cut the incidence of CV death, MI, or stroke.

PEGASUS-TIMI 54 enrolled 21,162 patients who were 1-3 years out from a prior myocardial infarction at 1,161 sites in 31 countries. Enrolled patients also had to be at least 50 years old, and have at least one additional risk factor for ischemic events such as age 65 years or older, diabetes, multivessel coronary artery disease, or chronic renal dysfunction. The enrolled patients averaged 1.7 years out from their index MI. Randomization assigned patients to treatment with 90 mg ticagrelor b.i.d., 60 mg ticagrelor b.i.d., or placebo, and all patients also received daily treatment with 75-150 mg aspirin.

After a median follow-up of 33 months on treatment, the combined rate of cardiovascular death, myocardial infarction, or stroke – the study's primary endpoint – occurred in 7.85% of patients on the 90-mg ticagrelor dosage, 7.77% of those on the 60-mg dosage, and 9.04% of patients on placebo receiving aspirin only, statistically significant differences for the study's primary endpoint for each of the two ticagrelor dosages.

Concurrent with the report at the meeting, the results also appeared online (N. Engl. J. Med. 2015; [doi:10.1056/nejmoa1500857]). The findings translated into hazard ratios of 0.85 for the 90-mg dosage and 0.84 for the 60-mg dosage, compared with placebo.

The study's primary safety outcome was the incidence of TIMI major bleeding events, which occurred in 2.60% of patients on the higher ticagrelor dosage, 2.30% of those on the 60-mg dosage, and 1.06% of those on placebo, which converted into hazard ratios of 2.69 for the 90-mg dosage and 2.32 for the lower dosage for TIMI major bleeds, compared with aspirin alone.

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VIEW ON THE NEWS

Post-MI patients need long-term secondary prevention

The results from PEGASUS-TIMI 54 provide a powerful message for secondary prevention: Patients who have had a prior myocardial infarction remain at an increased risk for subsequent ischemic events, even when maintained on what is currently standard therapy and even when they are several years out from their event.

We have no perfect antiplatelet drugs. Treating patients like those enrolled in the trial with an agent like ticagrelor further reduced their risk for ischemic events, but at the price of increasing their risk for major bleeds. The good news was that the rates of fatal bleeds and intracranial hemorrhages did not increase with ticagrelor treatment. Selecting the right patients to treat with prolonged dual-antiplatelet therapy (DAPT) requires good judgment as well as understanding the patient's values and preferences. From the clinician's perspective, it is the fatal bleeds or intracranial hemorrhages that are most comparable to cardiovascular deaths, myocardial infarctions, or strokes. Although I do not want to minimize the impact of other major or minor bleeds that might require transfusions, these are not considered as important for patient well-being as the ischemic events that ticagrelor treatment reduced.

I believe that the findings from PEGASUS-TIMI 54 will work their way into everyday practice with clinicians increasingly keeping patients on prolonged DAPT following percutaneous coronary interventions or a myocardial infarction. Problems with bleeding or dyspnea usually appear relatively early for patients on DAPT. The new findings give us increased confidence that once these patients get to a year out from the onset of treatment, they can safely continue treatment and derive ongoing benefit from it, especially higher-risk patients, even though the 60-mg formulation of ticagrelor is not currently available. The new results complement those reported last year from the DAPT trial, which also addressed the safety and incremental value of more prolonged DAPT for higher-risk MI and acute coronary syndrome patients.

Dr. Richard C. Becker is professor and director of the University of Cincinnati Heart, Lung, and Vascular Institute. He has been a consultant to and received research grants from AstraZeneca, the company that sponsored PEGASUS-TIMI 54 and that markets ticagrelor (Brilinta). He made these comments in an interview.

FROM THE EVP/CEO: Solutions to make your tomorrows > today

BY PAUL A. MARKOWSKI, CAE

As a membership organization, CHEST is committed to supporting you and offering solutions that can make your tomorrows greater than today. It's incumbent on us to ensure you continually derive value from our organization, and that's the motive that led us to implement a robust, new association management software (AMS) system to improve and simplify the way you engage with us online. The AMS is scheduled to go live the first week of May, so I'd like to share what that will mean for you.

The main benefit you'll notice is single sign-on. Single sign-on is a feature that connects related, but independent, software systems, so a user can log in once and access all systems without needing to log in repeatedly for each individual system. Today, you're required to log in to each of our systems separately. Single sign-on will connect the systems for our store, Learning Site, CME claiming, event registration, hotel reservations, session submission, and conflict of interest disclosure. When you log in to any of these systems, you'll have access to all of them without needing to log in again. You'll be able to move from one system to the next without interruption for signing in.

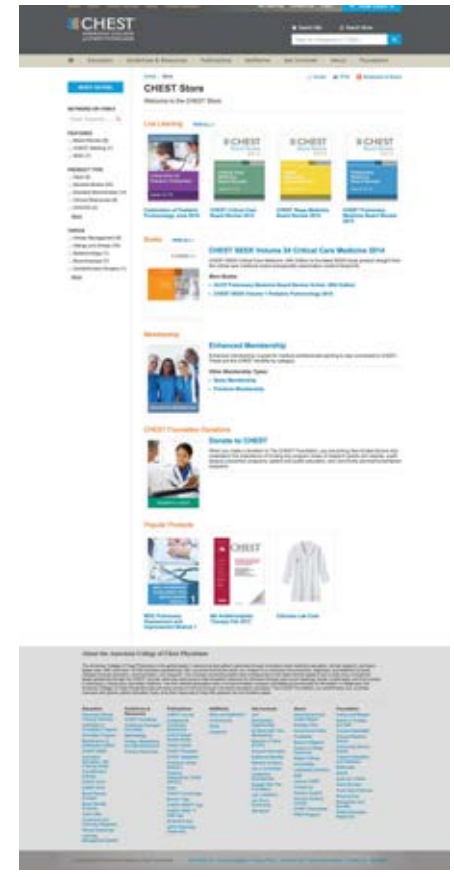

MR. MARKOWSKI

For the most part, you won't see many changes to chestnet.org after the AMS is live. The interface will remain very familiar—until you visit the store. Our online store has had a major facelift! You'll immediately notice cleaner, more attractive page designs and more intuitive navigation. And, new to the store is an easy way to renew your CHEST membership. If you have trouble finding what you're looking for, the upgraded search feature will allow you to filter results with further refinement. You'll be able to limit your search to the store only or continue to search across chestnet.org, the journal *CHEST*, and our meeting sites. It will be an improved experience, offering popular features similar to other retail sites.

The CHEST staff has been committed to implementing the AMS, working hard for many months. They've developed, designed, trained, tested, and debugged to deliver a better experience for you come May. Despite this skilled and careful work, it's realistic to expect there may be initial hiccoughs after the AMS goes live. If you experience any difficulty whatsoever, I encourage you to contact our Customer Support team at chestcustomersupport@chestnet.org, 800/343-2227, or 224/521-9800. They're top notch and will be ready to help you resolve your issues.

I'm looking forward to going live with the AMS in May. But, I don't think of that day as our finish line, marking the end of months of intense development. Rather, it's our starting line, marking the beginning of improved online solutions to enhance your engagement with us. And, since it's only the beginning, you can expect that we'll continue our work to help you achieve more through improved access to information and resources online. It's our way of offering solutions to help make your tomorrow greater than today.

Check out the new AMS features next month, and let me know what you think. And, as always, I invite you to follow me on Twitter (@PMarkowskiACCP), or look for me at upcoming CHEST events.



Experience Montréal's past, be part of chest medicine's future

Montréal, Canada, will welcome the CHEST Annual Meeting 2015, October 24 – 28, and it couldn't be more appropriate.

Montréal will set a perfect backdrop of old world charm mixed with North American energy. CHEST will fit right in with over 8 decades of clinically relevant annual meetings and its exciting schedule of innovative, state-of-the-art educational opportunities. You may come for the education, but you won't want to leave without exploring this charming city.

Just minutes away from the Palais des congrès de Montréal, the convention center, Old Montréal offers a glimpse into Montréal's history blended with hip, urban hotspots. Complete with cobblestone paths, chic art galleries, 19th century architecture, and trendy boutiques, this neighborhood will keep you busy during your spare time.

Start planning your itinerary today with these recommended spots in Old Montréal:

• Visit Notre-Dame Basilica. This Gothic Revival style church was built between 1672 and 1683. Admire the dramatic architecture and colorful interior as you take a guided tour to learn about the history, architecture, and much more.

• Go shopping and dine at Marche Bonsecours. This historic building is home to galleries, boutiques, and restaurants. You'll recognize it's imposing silver dome in this historic district.

• Explore the outdoors at The Quays of the Old Port, a park that runs alongside the St. Lawrence River. You'll find festivals and cultural events. Plus, there are walking paths, restaurants, and terraces with beautiful views of the city.

• Learn about local history at the Pointe-a-Calliere, Montréal Museum of Archaeology and History. This national historical and archaeological site leads visitors through centuries of history.

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Notre-Dame Basilica, Montréal

• Visit Chateau Ramezay, a private museum that details the history of Québec and Montréal.

• Dine at Olive & Gourmando. While there is regularly a line to get into this cafe, the cuisine is worth the wait. You'll enjoy creative sandwiches, local beer and wine selections, and pastries galore!

After you visit the past in Old Montréal's historic neighborhood, you'll find yourself recharged and ready for the latest in pulmonary, critical care, and sleep medicine education. CHEST 2015 will give you a glimpse into the future of chest medicine with the latest guidelines, abstracts, and simulation education. Find everything you need to know to make the best clinical decisions and inspire your patient care. Learn more at chestmeeting.chestnet.org.

New publisher chosen for *CHEST*

Elsevier, a world-leading provider of scientific, technical, and medical information products and services, and the American College of Chest Physicians (CHEST), a world-renowned publisher of evidence-based practice guidelines in chest medicine, have announced that Elsevier will publish the organization's flagship journal *CHEST* as of January 1, 2016. This significant and exciting piece of news that will positively affect the future of the journal is a licensing agreement, wherein CHEST retains all ownership of the journal, copyright, trademark, and editorial decision-making. Elsevier's role will be heavily focused on the business and operational aspects of publishing the journal and will provide significant resources to help us continue to take *CHEST* to a higher level.

"We are excited to begin this new relationship with Elsevier and we look forward to *CHEST*'s continued success under this collaboration," said Paul Markowski, CEO and Executive Vice President of the American College of Chest Physicians. "*CHEST* will remain a leading publication designed to aid clinicians in providing the best patient care possible."

Dr. Richard Irwin, Master FCCP, and Editor in Chief, said, "Our publishing agreement with Elsevier will allow *CHEST* to remain competitive, will help us to distribute research papers to a larger audience, and will allow us to better attract higher profile clinical research from around the world. We anticipate many enhancements to the journal, which will benefit our authors, members, and readers."

The relationship with Elsevier will allow *CHEST* to leverage the global capabilities of Elsevier, its ScienceDirect platform, and its new ClinicalKey service to distribute the journal to an even larger audience than ever and attract higher profile research from around the world.

CHEST Foundation grants – April 30th deadline is approaching!

Medical research grants have contributed to medical discoveries and innovations all over the world.

Milestone research projects, such as immunizations, pollutant quality control, 3D bioprinting technologies, and even public education programs and resources, have all been funded at one time or another by generous donations.

The results of those donations lead to amazing impacts on the medical profession and on patients' lives.

The CHEST Foundation contributes to advancing medical research and public education by providing our members with a variety of research grants and a community service grant.

Applications are now being accepted, and the April 30 deadline is approaching.

Apply today!
chestnet.org/grants
Help future grants by donating today!
chestnet.org/donate

CHEST membership is moving forward to better serve you

TOMORROW > TODAY

We asked you, and you told us what you need to make your tomorrows greater than today.

That's why we're upgrading our membership philosophy and structure starting this May, allowing you to:

• **Collaborate more** with integrated programming and CHEST membership available to all members of your clinical care team.

• **Engage more** by choosing the membership level that gives you the benefits you want.

• **Achieve more** with streamlined access to our online systems, making it easier than ever to tap into the wealth of resources CHEST offers you.

Learn more about the new membership model at chestnet.org/tomorrow. See videos of Dr. Curtis N. Sessler, FCCP, CHEST President, explaining why we're changing the membership model, and Paul Markowski, CHEST EVP/CEO, describing the benefits of the three levels of membership.

Get answers to commonly asked questions, and, if your question isn't answered there, submit a question of your own.

Visit now to find out how your CHEST membership can help make your tomorrows greater than today.

Catching up with Past Presidents: Dr. James B.D. Mark

Where are they now? What have they been up to? CHEST's Past Presidents each forged the way for the many successes of the American College of Chest Physicians (CHEST), leading to enhanced patient care around the globe. Their outstanding leadership and vision are evidenced today in many of CHEST's current initiatives, and now it is time to check in with these past leaders to give us a look at what's new in their lives.

James B.D. Mark, MD, FCCP
President 1994-1995

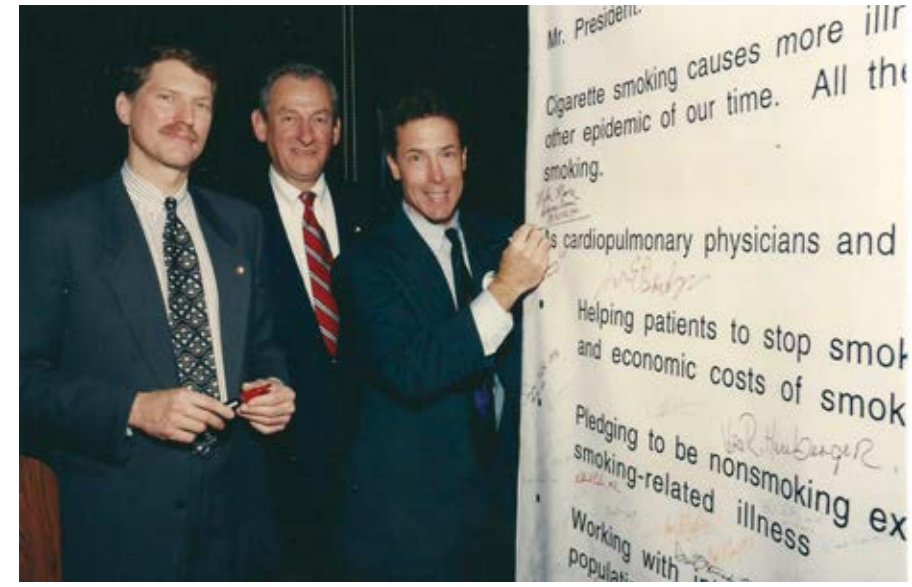
My presidential year began in New Orleans at CHEST 1994. The welcoming reception, which was Halloween-themed, started the year off with a bang. Attendees were encouraged to wear costumes and many did so. Two robbers, complete with trick-or-treat bags and masks. crashed the party and helped themselves to unattended purses and more. They were caught in the act by one of the guests and turned over to the New Orleans police. ... and the year just got better!

Two highlights were travel to the Asia-Pacific Congress on Diseases of the Chest in Hong Kong and to the meeting of the European Respiratory Society in Barcelona. The delegation from the ACCP was well received at both meetings.

Memorable, also, was a leadership luncheon meeting with the American Thoracic Society in Seattle. Dr. Claude Lenfant, Director of the NHLBI, attended the luncheon. He said at the time that he had given many talks to lay and professional groups over the years and that during the question-and-answer periods, he had never had a question asked about lung disease, only heart disease, the clear implication being that we "Lungies" better get our message out to the public. Interacting with the staff of the ACCP and many members of leadership during the year was a stimulating and memorable experience.

I am currently Professor of Cardiothoracic Surgery, Emeritus at Stanford University School of Medicine. I achieved Emeritus status at Stanford in 1996, but continued to operate for another year and be active clinically for several more years. I no longer see patients but do attend conferences each week. I go to few professional meetings, national or international, but do travel with my wife and family. A highlight was a trip to Rwanda, Kenya, and Tanzania recently.

My exercise regimen includes walking, going to the gym for light workouts, and playing golf. Where but the Stanford Golf Course can a previous Heisman Trophy winner, Jim Plunkett, be in the foursome ahead of you and an ex-Secretary of State, Condoleezza Rice, be in the one behind you?



Dr. Mark (center), flanked by Tom Glide, of Blue Cross/Blue Shield of Minnesota (left), and Mike Moore, Attorney General of Mississippi (right), who was the Keynote Speaker at CHEST 1994.

James B. D. Mark, MD, FCCP
Professor of Cardiothoracic Surgery, Emeritus
Stanford University School of Medicine
President, American College of Chest Physicians, 1994-1995

Sarcoidosis patient education campaign

In honor of National Sarcoidosis Awareness month, the CHEST Foundation and Foundation for Sarcoidosis Research (FSR) have launched ***Sarcoidosis: Seek Answers. Inspire Results.***, a nationwide campaign encouraging patients with sarcoidosis to take a proactive role in their treatment plan (www.stopsarcoidosis.org/patient-resources/what-is-sarcoidosis).

This rare, autoimmune disease, which affects the lungs in 90% of cases, can often mimic other conditions as well, further adding to the complexity of the disorder. For instance, sarcoidosis can mimic fungal or mycobacterial infections, chronic beryllium disease, hypersensitivity pneumonitis, rheumatologic syndromes, lymphoma, tumor-associated granulomas, pulmonary fibrosis, and more. Lung symptoms often include a cough that does not go away, shortness of breath, and chest pain. About one-third of patients will also experience nonspecific symptoms, such as fever, fatigue, weight loss, night sweats, and an overall feeling of ill health. Key diagnostic tools include chest radiographs, laboratory blood tests, breathing tests, and a biopsy.

Anyone can develop sarcoidosis; however, for reasons not yet understood by medical science, the condition is more prevalent among African-Americans and people of Northern European – particularly Scandinavian – descent. Sarcoidosis most commonly occurs among people between the ages of 20 and 40.

If diagnosed and under good medical care, most cases of sarcoidosis have a positive prognosis and do not cause lasting damage to the body. However, 30% to 40% of people living with sarcoidosis have a persistent condition that may require personalized treatment – including co-consultation with other organ specialists, as indicated – to control symptoms.

To this end, the ***Seek Answers. Inspire Results.*** campaign encourages physician/patient dialogue, as well as treatment compliance. For educational tools to share with patients, including the "Sarcoid Five" – five questions designed to jumpstart physician/patient conversations – visit chestnet.org/sarcoid.

Patient education resources supported in part by a grant from Mallinckrodt Pharmaceuticals Autoimmune and Rare Diseases.

For further reading:

www.stopsarcoidosis.org/patient-resources/what-is-sarcoidosis/
www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/pulmonary/sarcoidosis/Default.htm#ceboxtext3
www.chestnet.org/Foundation/Patient-Education-Resources/Sarcoidosis
www.stopsarcoidosis.org/patient-resources/faqs/

This month in *CHEST:* Editor's picks

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

Nighttime Intensivist Staffing, Mortality, and Limits on Life Support: A Retrospective Cohort Study.
By Dr. M. P. Kerlin et al.

Hospital Discharges, Readmissions, and ED Visits for COPD or Bronchiectasis Among US Adults: Findings From the Nationwide Inpatient Sample 2001-2012 and Nationwide Emergency Department Sample 2006-2011.
By Dr. E. S. Ford

Ultrasound-Guided Medical Thoracoscopy in the Absence of Pleural Effusion
By Dr. G. Marchetti et al.

Giants In Chest Medicine
Honoring Dr. Jay A. Nadel

Medical Ethics
The Uncommon Case of Jahi McMath
By Dr. J. M. Luce

Evidence-Based Medicine
Executive Summary: Prevention of Acute Exacerbation of COPD: American College of Chest Physicians and Canadian Thoracic Society Guideline (Podcast available.)

Prevention of Acute Exacerbations of COPD: American College of Chest Physicians and Canadian Thoracic Society Guideline (Podcast available.)

NETWORKS: Environmental health, palliative care, sleep medicine, respiratory care

Occupational and Environmental Health

Time to part the smoke screen: women and children first

Almost 3 billion individuals use solid fuels for heating and cooking, leading to very high levels of household air pollution. In a recent study comparing traditional clay "chulha" cook stoves and alternative cook stoves, there was a significant decrease in particulate matter (PM)2.5 and CO concentration (Muralidharan et al. *Int J Environ Res Public Health*. 2015;12[2]:1773).

DR. HARANATH

However, none of the cook stoves met the WHO standards that recommend a PM2.5 level below 25 μg/m³ particulate matter exposure. Indoor air pollution contributes to nearly 2 million deaths annually, with women disproportionately more affected, possibly from greater exposure. To address this major problem, the Global Alliance for Clean Cookstoves has a goal of reaching 100 million households by 2020 (Martin et al. *Science*. 2011;334[6053]:180). While outdoor air pollution is well-known, newer sources, like fracking, are only now being evaluated. The impact of air pollution and its management is inadequately studied despite the morbidity and mortality issues. In fact, searching clinicaltrials.gov using the keyword "air pollution" only shows 18 open studies (11 from North America). Encouragingly, there was recent evidence for reversal of decline in lung function in children who had a decrease in exposure to air pollutants (Gauderman et al. *N Engl J Med*. 2015;372[10]:905). Clearly, there is an urgent need for engagement on the air we breathe around the world. Our NetWork plans to have sessions on these themes at CHEST 2015.

Dr. Sai Praveen Haranath, MPH, FCCP
Steering Committee Member

Palliative and End-of-Life Care

Palliative care as a train station

Have you ever struggled to explain palliative care to a patient or family? My mentor taught me to describe palliative care as a train station. Typically, a patient's symptoms and findings lead to tests and then treatments. Before they know it, patients are on an express train that is equipped to get them the best medical care possible. However, the train doesn't feel like it's under their control, and it has considerable momentum. In intensive care, the train is more like a roller coaster.

DR. KREGENOW

Similar to a train stopping to refuel and exchange passengers, a palliative care consult is a chance for a patient, family, and medical provider to get off the train and do two important things. First, we find the bathroom and sandwich shop, a metaphor for addressing symptoms. Second, we look at the map and examine where we've been and where we are headed. What was our destination? Is this train still headed in the right direction? Sometimes this visit to the train station leads to a change in itinerary; other times it just helps patients and families stay fed and warm. This pause helps everyone make sure the path we're on is one that fits with the stated goals and keeps quality of life in perspective. Despite the growing awareness of palliative care, the average person has difficulty understanding the specialty until they experience it. With the train station metaphor, I find myself able to move past the description of palliative care and into a therapeutic conversation.

Dr. David Kregenow
Steering Committee Member

Sleep Medicine

OSA, snoring, and oral appliances

With increasing treatment options and a growing population of patients diagnosed with sleep-disordered breathing, the treatment of OSA is becoming more and more of a multidisciplinary field. Patients with OSA now have the options of CPAP therapy, oral appliances, negative oral pressure therapy, nasal expiratory airflow resistance devices, or surgical treatment options, including hypoglossal nerve stimulators and even weight loss surgery. Therefore, patients may be identified and managed by sleep specialists, dentists, surgeons, and other physicians. As a multidisciplinary approach becomes more common, updated guidelines will be necessary.

DR. DAS

Oral appliance therapy (OAT) to treat OSA has been an area of extensive research over the past several years. We have some data for improved cardiovascular outcomes with use of OAT for OSA. In 2002, the American Academy of Dental Sleep Medicine had 300 members, and now the association has over 2,700 members. More and more dentists are the initial caregivers who identify a patient at risk for OSA. Collaboration with sleep specialists should be encouraged in these situations for appropriate assessment of OSA severity and comorbid sleep disorders. Together, the sleep specialist and dentist can determine the best treatment for the patient and ensure adequate efficacy.

A new guideline for the treatment of OSA and snoring with oral appliances is forthcoming from the American Academy of Sleep Medicine and American Academy of Dental Sleep Medicine. Physicians, dentists, and organizations, such as the Sleep NetWork Steering Committee of CHEST, have been asked to give input on the existing draft (www.aasmnet.org/articles.aspx?id=5362).

Dr. Aneesa Das, FCCP
NetWork Chair

Respiratory Care

Keeping the lunger out of the house: what's new in preventing COPD readmissions?

In 2015, CMS added COPD to core measures used to calculate hospital risk-adjusted readmission rates. Up to 3% of total Medicare payments are at risk, and FY15 data indicate that three-fourths of eligible hospitals are being penalized, with an average penalty of 0.63% (http://kaiserhealthnews.org/news/medicare-readmissions-penalties-2015). COPD has readmission rates of up to 25% and is an independent risk factor for other medical readmissions.

DR. O'NEIL

Despite considerable interest in reducing COPD readmissions, there is little to guide pulmonologists and hospitals. CHEST and the Canadian Thoracic Society recently published guidelines for preventing AECOPD (Criner et al. *CHEST*. [Published ahead of print Oct 16, 2014]), although not specifically focused on readmissions. *CHEST* also recently published a systematic review of self-management following AECOPD (Harrison et al. *CHEST*. 2015;147[3]:646), and NAMDRC reported recommendations from a 2014 multisociety conference (www.namdrc.org/pubs/ HospitalReadmissions.pdf). Recent single institution studies (Hijjawi et al. *Postgrad Med*.[Published ahead of print Feb 17, 2015]) (Jennings et al. *CHEST*. [Published ahead of print Dec 24, 2014]), and an analysis of Medicare claims data (Shah et al. *CHEST*. [Published ahead of print Dec 24, 2014]) confirm the importance of COPD severity, comorbidities, and social/financial factors in readmissions. While AECOPD is the most common cause of readmission, half of the readmissions are nonpulmonary. The studies suggest that programs focused only on pulmonary disease are unlikely to be successful and that a multidisciplinary approach also addressing financial and psychosocial issues is needed.

Current interest has focused on patient navigators. Nursing models applied to outpatient populations have demonstrated reductions in hospitalizations and ED visits but didn't address readmissions (Dajczman et al. *Can Respir J*. 2013[5]:351). Preliminary data using respiratory therapists (RTs) as COPD navigators have shown promise (http://respiratory-care-sleep-medicine.advanceweb.com/Features/Articles/COPD-Navigators.aspx), but, clearly, additional work and innovative approaches will be needed to significantly reduce COPD readmissions.

The Respiratory Care NetWork will examine the role of the RT in preventing COPD readmissions with its featured speaker presentation at CHEST 2015 in Montréal.

Dr. Kevin O'Neil, FCCP
NetWork Chair

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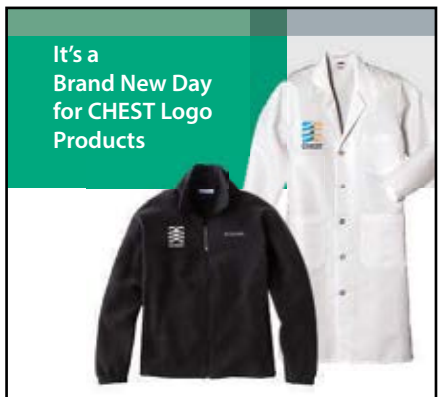

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John Baltazar
Tel: (917) 488-1528
jbaltazar@americanmedicalcomm.com

FRONTLINE MEDICAL COMMUNICATIONS

UNIVERSITY of COLORADO HEALTH

Fort Collins, Colorado

Colorado Health Medical Group is seeking a Pulmonologist/Critical Care trained physician. Sleep Medicine training desirable but not required. Will rotate in two hospitals and our Loveland based clinic. Call is 1:11 nights and 1:5-6 weekends. Physician will be doing general Pulm/CC procedures and read sleep studies from outlying facilities.

If interested, email your CV to Briann.Leone@uchealth.org

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If contributing to a team with an expectation for excellence and creating a balanced and fulfilling life are important to you, St. Vincent Healthcare in Billings, Montana has the opportunity and community for you!

St. Vincent Healthcare in Billings, Montana seeks U.S. trained BE/BC certified physician for our **Pulmonology** Center

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Central Maine Medical Center
The Central Maine Medical Family

Inpatient Pulmonary/Critical Care Position in Maine:

Join a vibrant Inpatient Pulmonary and Critical Care group of five in beautiful Maine! Central Maine Medical Center (CMMC) is seeking a BC/BE Pulmonary/Critical Care Physician to help provide pulmonary and critical care services to medical, surgical, trauma, and cardiac patients.

CMMC is a 250 bed, full service regional referral center with busy trauma, cardiothoracic, interventional radiology, vascular, and neurosurgical programs. We have a state-of-the art 19 bed ICU and a separate 16 bed cardiothoracic unit.

Competitive salary and benefits including CME, paid vacation, student loan repayment, 403b match, and relocation fees. Work schedule revolves around a 6 day on and 6 day off philosophy, with no longer than 12 hour shifts per day. There is no outpatient clinic work.

Residents and visitors enjoy an extraordinary lifestyle that revolves around top school systems, ski resorts, lake and ocean water sports, theatre, and world-class dining.

Interested applicants may submit CV to Julia Lauver, Medical Staff Recruiter, Central Maine Medical Center, 300 Main Street, Lewiston, ME 04240. Email: JLauver@cmhc.org . Fax: 207/795-5696. Call: 800/445-7431. Visit our website, www.cmmc.org.

Cardiac Intensivist

OPPORTUNITY IN SOUTH FLORIDA

Memorial Healthcare System is seeking critical care physicians, dedicated to night shifts, to join the critical care team. Successful candidates will demonstrate excellent clinical skills, a broad knowledge base in critical care and dedication to providing high-quality, evidence-based care. Applicants must be BC/BE in critical care medicine. Previous experience in managing cardiac surgery patients is a plus but not a requirement. Physician(s) would have exposure to all aspects of the care of cardiac surgery patients, including mechanical devices, advanced heart failure patients, ECMO and transplant.

- 12-hour in-house shifts (7pm-7am)
- No responsibilities outside of in-house shifts
- Approximately 15 shifts per month (more if desired)
- Highly-competitive salary differential for the nocturnist position

These are full-time employed positions within the multi-specialty Memorial Physician Group. The positions offer competitive benefits and a compensation package that is commensurate with training and experience. Professional malpractice and medical liability are covered under sovereign immunity.

Memorial Healthcare System

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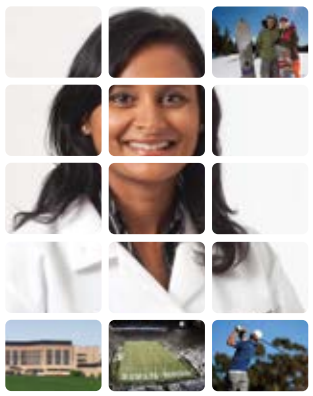

Mount Nittany Health Pulmonologist Opportunity

Mount Nittany Physician Group is seeking a pulmonologist to join its growing practice. The group is physician-led and professional managed with more than 120 employed providers in 23 specialties. The Physician Group and Mount Nittany Medical Center, a 260 bed acute care hospital are of Mount Nittany Health, a growing health system serving central Pennsylvania.

Our 6-physician pulmonary practice currently provides a range of pulmonary medicine services including interventional procedures, allergy/immunology, and sleep medicine, as well as outpatient pulmonary medicine/procedures and inpatient pulmonary consults.

State College, Pa., is home to The Pennsylvania State University, one of the nation's largest educational institutions. Affectionately nicknamed "Happy Valley," our vibrant college town offers a diverse culture, a beautiful natural environment, excellent public and private schools, affordable real estate, countless options for dining, theatre, sports and recreation, nightlife and more. This is all located within a safe, friendly community that makes the area perfect for raising a family.

MOUNT NITTANY HEALTH

Contact:
Lorelei Shaw, Director of Physician Recruitment
814.278.4866 | lshaw@mountnittany.org
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Critical Care Medicine Nocturnist

OPPORTUNITY IN SOUTH FLORIDA

Memorial Healthcare System's Intensivist Program has expanded. The program is currently comprised of 23 full-time intensivists and five critical care ARNPs, providing 24/7 ICU coverage at multiple locations within the Memorial Healthcare System. In addition to critical care, many of our intensivists hold multiple board certifications including infectious diseases, pulmonology, surgery and neuro-critical care.

The available positions are full-time employed positions with competitive benefits and compensation package, sovereign immunity, paid CME and state-of-the-art equipment (including EPIC EHR, digital Olympus bronchoscopes, intubation scopes, Glidescopes, Sonosite Ultrasounds, etc.).

Qualifications & Responsibilities:
The program is seeking dedicated critical care nocturnists to join the existing team. The nocturnists will integrate into the existing operational structure as the program expands to cover additional critical care units. Critical care coverage is provided in 12-hour in-house shifts, 7pm to 7am, averaging approximately 15 shifts per month. The successful candidates will demonstrate excellent clinical skills, a broad knowledge base in critical care and dedication to providing high-quality, evidence-based care. Candidates must be BC/BE.

Memorial Healthcare System

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Tel: (917) 488-1528
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FRONTLINE MEDICAL COMMUNICATIONS

MASSACHUSSETTS

Pulmonary/Critical Care Opportunity, North of Boston

A close affiliate of Massachusetts General Hospital, North Shore Medical Center and North Shore Physicians Group, seek a Pulmonary and Critical Care physician (Sleep optional) to join the busy and growing Division of Pulmonary, Critical Care, and Sleep Medicine.

NSMC is an academic community hospital near Boston.

Generous compensation and fringe benefits (including malpractice insurance) with teaching opportunities.

No night ICU call.

Interested candidates must be BC/BE in both Pulmonary and Critical Care Medicine (Sleep optional) and should forward their CV to:

Louis Caligiuri, Director,
Physician Services at
lcaligiuri@partners.org

ILLINOIS

Four member pulmonary/critical care group in Chicago seeks 5th. Based in large urban teaching hospital with pulmonary fellowship program, Division part of large multi-specialty hospital affiliated group. Closed ICU, sleep lab/clinic.

Must be BC/BE in Pulm/CCM. Sleep experience a plus. Compensation/Benefits competitive. Contact Joseph Rosman, MD **rosj@sinai.org** or 847 721 3817

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Asthma exacerbations reduced by 20%

ICS/LABA *from page 1*

including a large safety study that addressed safety concerns associated with LABAs in the treatment of asthma.

At the March 19 joint meeting of the FDA's Pulmonary-Allergy Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee, the panels voted 16-4 that the efficacy and safety data supported the approval of both proposed doses in adults.

Many panelists noted the benefit of having a once-daily inhaled treatment to treat asthma, which could improve compliance. Most agreed that the efficacy data in adults provided a substantial amount of evidence that the two doses had a "clinically meaningful benefit" in adults, with beneficial effects on lung function and exacerbation rates.

But the panelists voted 19-1 that the data did not support approval in adolescents aged 12-17 years. Members expressed uncertainty about safety in adolescent subjects, who were studied in the same trials as were adults.

In addition, study data indicated that the combination's beneficial effects were no better than those of fluticasone alone, panelists said. They also noted a numerical imbalance in hospitalizations among adolescents in a large safety study, and they pointed to the availability of other treatments for that age group.

Panelists voting no also said the efficacy results in adolescents were inconsistent, with "no clear trends in the positive direction," as one panelist noted. Furthermore, there was no evidence that the combination of fluticasone and vilanterol at either dose was more effective than the ICS alone on forced expiratory volume in 1 second or asthma exacerbations.

Panelists also cautioned that the positive results in adults, who made up the majority of patients enrolled in the studies, could not be extrapolated to adolescents. Thus, there was a need for a separate safety and efficacy study in adolescents.

"At least in the adults, it offers something, perhaps the additional benefit of better compliance," said the panel chair, Dr. Erik Swenson, professor of medicine and physiology, pulmonary and critical care medicine, University of Washington, Seattle.

The combination also was superior at both doses at improving lung function and reducing exacerbations.

But among patients age 12-17 years, "there seems to be no obvious superiority and possibly inferiority against just fluticasone alone," Dr. Swenson said.

Considering that results of large, ongoing LABA safety trials may soon become available, "I don't feel comfortable adding a new LABA to the mix right now," said Dr. Judith Kramer, professor emerita of medicine, Duke University, Durham, N.C., who voted against approval both for pediatric and adult patients.

Because it is taken once a day, the combination's main advantage would be adherence, Dr. Kramer added. But "it's not adding any major new therapeutic benefit, and there is the safety concern in the adolescents, and there may well be off-label use."

Given longstanding concerns about serious asthma-related events associated with LABAs – particularly in pediatric and black patients – the FDA has required manufacturers to conduct postmarketing safety studies evaluating the risks of LABAs when added to an ICS.

Those studies include a GSK study of more than 11,000 patients aged 12 years and older evaluating the safety of Advair, a combination of fluticasone and the LABA salmeterol. Results from that study could be available in early 2016.

For the fluticasone-vilanterol asthma indication, GSK submitted the results of two 12-week and one 24-week lung function studies, enrolling a total of about 2,200 patients whose mean age was 44 years (about 8% were aged 12-17 years).

Another study evaluated the time to first asthma exacerbation in more than 2,000 patients, which included almost 300 patients aged 12-17 years. In that study, the risk of asthma exacerbations was reduced by about 20% among those on the combination, compared with those on fluticasone alone. There were no intubations or deaths from asthma exacerbations.

But in a subgroup analysis of patients aged 12-17 years, conducted by the FDA, the risk of asthma exacerbations was higher among those treated with fluticasone-vilanterol, compared with patients 18 years and older.

In addition, an FDA meta-analysis of asthma-related serious adverse events in the four studies found a numerical imbalance in hospitalizations among adolescents: four hospitalizations among those on the combination drug, but none on fluticasone alone.

If approved, fluticasone-vilanterol would be the first once-daily inhaled ICS/LABA combination treatment for asthma. Fluticasone (100 mcg and 200 mcg) is approved for treating asthma. Unlike the LABAs salmeterol and formoterol, however, vilanterol is not approved as a single agent. Vilanterol (as part of the combination product) would be the first new LABA approved for asthma in 15 years.

The FDA usually follows the recommendations of its advisory panels; a decision is expected by April 30. Panelists had no disclosures.

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FDA approves miniature heart pump for high-risk PCI

BY ELIZABETH MECHCATIE
Frontline Medical News

A miniature heart pump has been approved by the Food and Drug Administration to "help certain patients maintain stable heart function and circulation during certain high-risk percutaneous coronary intervention (HRPCI) procedures," the agency has announced.

The Impella 2.5 System, manufactured by Abiomed, is "intended for temporary use by patients with severe symptomatic CAD [coronary artery disease] and diminished (but stable) heart function who are undergoing HRPCI but are not candidates for surgical coronary bypass treatment," the FDA's statement said.

"Use of the Impella 2.5 System is intended to prevent episodes of unstable heart function, including unstable blood pressure and poor circulation, in patients who are at high risk for its occurrence," Dr. William Maisel, acting director of the Office of Device Evaluation in the FDA's Center for Devices and Radiological Health, said.

Approval was based on the PROTECT II study and observational data from the USpella Registry.

"The overall data provided evidence that, for patients with severe CAD and diminished heart function, the temporary circulatory support provided by the Impella 2.5 System during an HRPCI procedure may allow a longer and more thorough procedure by preventing episodes of hemodynamic instability ... due to temporary abnormalities in heart function," the FDA statement said. In addition, "fewer later adverse events" such as the need for repeat HRPCI procedures, "may occur in patients undergoing HRPCI with the pump compared to patients undergoing HRPCI with an intra-aortic balloon pump," according to the FDA.

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The system can be used as an alternative to the intra-aortic balloon pump without significantly increasing the safety risks of the HRPCI procedure. As a postmarketing requirement, the manufacturer will conduct a single-arm study of the device in high-risk PCI patients, the company said in a statement.

The wording of the approved indication is as follows, according to Abiomed: "The Impella 2.5 is a temporary (less than or equal to 6 hours) ventricular support device indicated for use during high-risk PCI performed in elective or urgent hemodynamically stable patients with severe coronary artery disease and depressed left ventricular ejection fraction, when a heart team, including a cardiac surgeon, has determined high-risk PCI is the appropriate therapeutic option. Use of the Impella 2.5 in these patients may prevent hemodynamic instability that may occur during planned temporary coronary occlusions and may reduce peri- and postprocedural adverse events."

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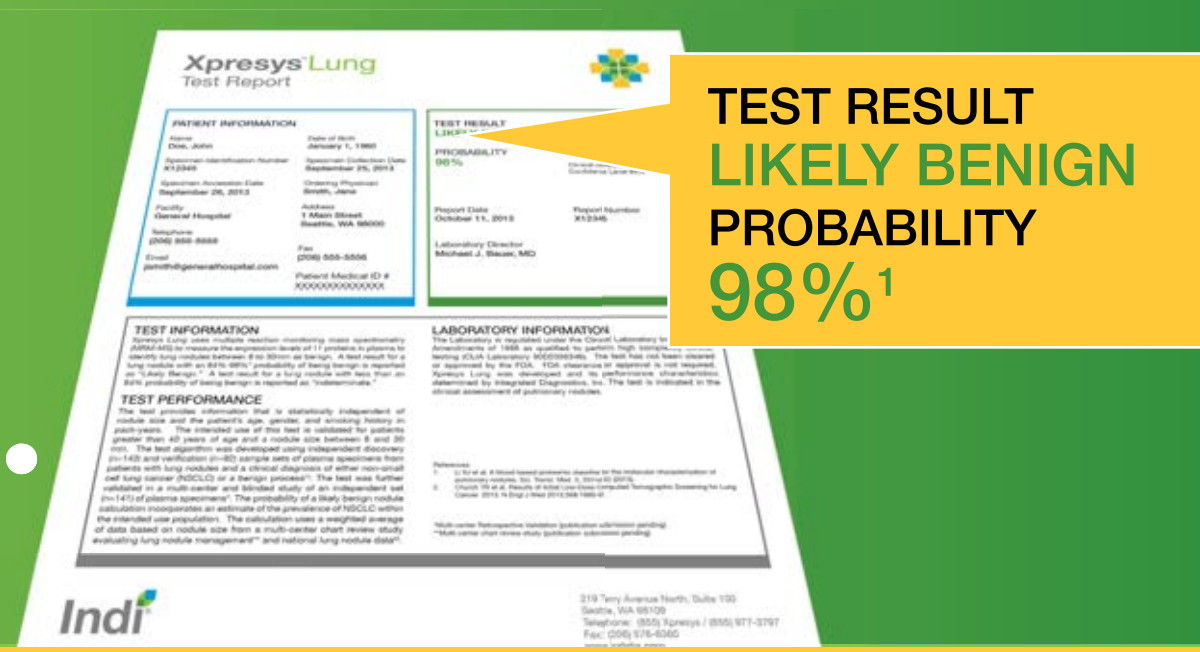

It is estimated **8.6 Million** Americans meet the guidelines for lung screening programs, resulting in an expected increase in benign nodules being identified. Xpresys Lung may be able to assist in more effectively managing these nodules and potentially avoid costly and invasive procedures.

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- Non-invasive blood test for pulmonary nodules
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