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CHEST™ Physician

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COURTESY JOHNS HOPKINS UNIVERSITY

Dr. Martin A. Makary says a training gap may explain some of the underutilization of minimally invasive surgery.

Open surgery or not? 'How' depends on 'where'

Minimally invasive surgery rates vary.

BY DOUG BRUNK

Frontline Medical News

The use of minimally invasive surgery for lung lobectomy, appendectomy, colectomy, and hysterectomy varies widely in the United States, even though the complication rates were lower from each procedure than with open surgery, results from a large retrospective study demonstrated.

"This study has important implications for quality improvement [QI]," researchers led by Dr. Martin A. Makary, professor of surgery at Johns Hopkins University, Baltimore, wrote in BMJ. "Based on our findings, many hospitals have an opportunity to decrease surgical complications by increasing utilization of minimally invasive surgery."

To investigate the levels of variation in the use of minimally invasive surgery across the United States, Dr. Makary and his associates used the National Inpatient Sample database, which is administered by the Agency for Healthcare Research and Quality, to evaluate hospitalizations at hospitals that performed at least 10 of these procedures in 2010. The sample included 1,051 hospitals in 45 states, and was limited to appendectomy, colectomy,

See **Quality** • *page 9*

Catheter-directed thrombolysis for leg DVTs held risky

More bleeds, three-fold higher costs.

BY MARY ANN MOON

Frontline Medical News

Catheter-directed thrombolysis plus anticoagulation is no more effective than anticoagulation alone in preventing in-hospital death among adults who have lower-extremity proximal deep vein thrombosis, according to a nationwide observational study reported in JAMA Internal Medicine.

However, catheter-directed thrombolysis carries higher risks, particularly serious bleeding risks such as intracranial hemorrhage, than does anticoagulation alone, and it costs nearly three times as much money. These findings highlight the need for randomized trials "to evaluate the magnitude of the effect of catheter-directed thrombolysis on … mortality, postthrombotic syndrome, and recurrence of DVT [deep vein thrombosis]. In the absence of such data, it may be reasonable to restrict this form of therapy to those patients who have a low bleeding risk and a high risk for postthrombotic syndrome, such as patients with iliofemoral DVT," said Dr. Riyaz Bashir of the division of cardiovascular diseases, Temple University, Philadelphia, and his associates.

See **Thrombolysis** • *page 9*

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CRITICAL CARE COMMENTARY

Micronutrients' role against sepsis

BY DR. MARY SANDQUIST AND DR. HECTOR R. WONG

The potential role of micronutrients in sepsis has created much recent interest and may offer novel therapies. Oxidant stress and inflammation are important components of sepsis pathobiology. Several micronutrients, notably zinc and selenium, are known to have antioxidant and anti-inflammatory properties and are, therefore, plausible candidates for adjunctive therapies in sepsis.

Selenium

Selenium plays a major role in the intra-

See **Micronutrients** • *page 25*

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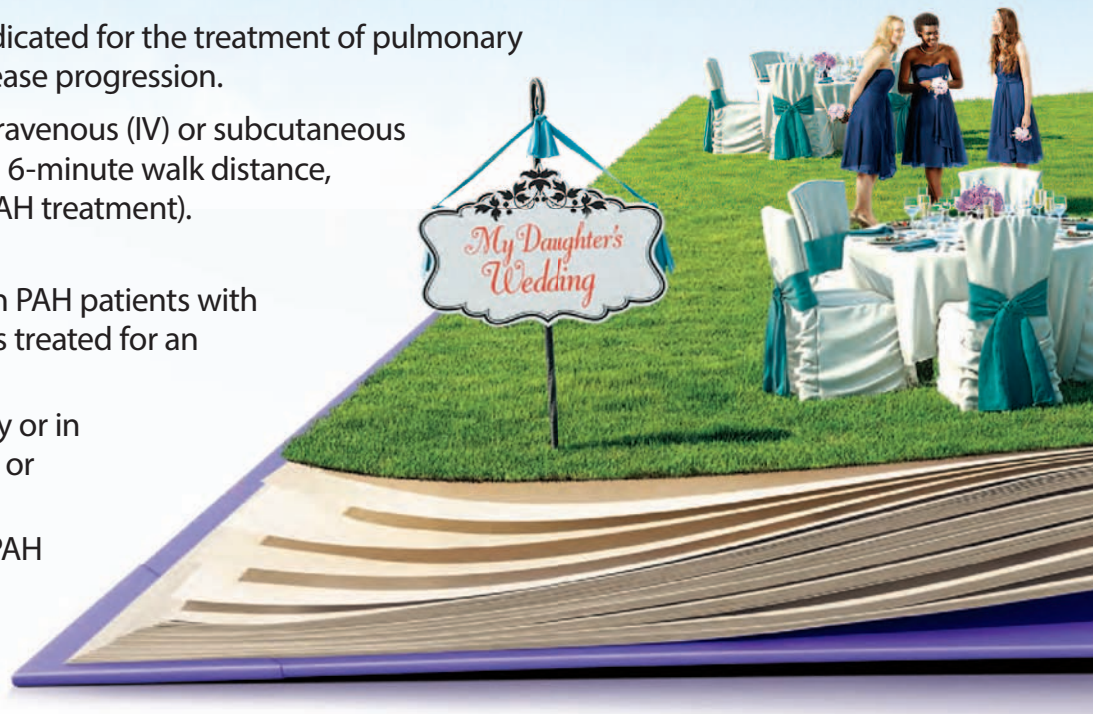
In the treatment of pulmonary arterial hypertension (PAH, WHO Group I)

HELP HER WRITE FUTURE CHAPTERS

Once-daily OPSUMIT® (macitentan) is the first and only oral PAH therapy indicated to both delay disease progression and reduce hospitalization for PAH

OPSUMIT is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression.

- Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment).
- OPSUMIT also reduced hospitalization for PAH.
- Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years.
  - Patients were treated with OPSUMIT monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids.
  - Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%).



IMPORTANT SAFETY INFORMATION

BOXED WARNING: EMBRYO-FETAL TOXICITY

- **Do not administer OPSUMIT to a pregnant female because it may cause fetal harm.**
- **Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception.**
- **For all female patients, OPSUMIT is available only through a restricted program called the OPSUMIT Risk Evaluation and Mitigation Strategy (REMS).**

CONTRAINDICATIONS

Pregnancy: OPSUMIT may cause fetal harm when administered to a pregnant woman. OPSUMIT is contraindicated in females who are pregnant. If OPSUMIT is used during pregnancy, apprise the patient of the potential hazard to a fetus.

WARNINGS AND PRECAUTIONS

Embryo-fetal Toxicity and OPSUMIT REMS Program

Due to the risk of embryo-fetal toxicity, OPSUMIT is available for females only through a restricted program called the OPSUMIT REMS Program. For females of reproductive potential, exclude pregnancy prior to initiation of therapy, ensure use of acceptable contraceptive methods, and obtain monthly pregnancy tests.

Notable requirements of the OPSUMIT REMS Program include:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the OPSUMIT REMS Program prior to initiating OPSUMIT. Male patients are not enrolled in the REMS.
- Females of reproductive potential must comply with the pregnancy testing and contraception requirements.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive OPSUMIT.

Hepatotoxicity

- Other ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. The incidence of elevated aminotransferases in the SERAPHIN study >3 × ULN were 3.4% for OPSUMIT vs 4.5% for placebo, and >8 × ULN were 2.1% vs 0.4%, respectively. Discontinuations for hepatic adverse events were 3.3% for OPSUMIT vs 1.6% for placebo.
- Obtain liver enzyme tests prior to initiation of OPSUMIT and repeat during treatment as clinically indicated.
- Advise patients to report symptoms suggesting hepatic injury (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching).
- If clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2 × ULN, or by clinical symptoms of hepatotoxicity, discontinue OPSUMIT. Consider re-initiation of OPSUMIT

Patient dramatization

when hepatic enzyme levels normalize in patients who have not experienced clinical symptoms of hepatotoxicity.

Hemoglobin Decrease

- Decreases in hemoglobin concentration and hematocrit have occurred following administration of other ERAs and in clinical studies with OPSUMIT. These decreases occurred early and stabilized thereafter.
- In the SERAPHIN study, OPSUMIT caused a mean decrease in hemoglobin (from baseline to 18 months) of about 1.0 g/dL vs no change in the placebo group. A decrease in hemoglobin to below 10.0 g/dL was reported in 8.7% of the OPSUMIT group vs 3.4% for placebo. Decreases in hemoglobin seldom require transfusion.
- Initiation of OPSUMIT is not recommended in patients with severe anemia. Measure hemoglobin prior to initiation of treatment and repeat during treatment as clinically indicated.

Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)

Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue OPSUMIT.

Decreased Sperm Counts

Other ERAs have caused adverse effects on spermatogenesis. Counsel men about potential effects on fertility.

ADVERSE REACTIONS

Most common adverse reactions (more frequent than placebo by ≥3%) were anemia (13% vs 3%), nasopharyngitis/pharyngitis (20% vs 13%), bronchitis (12% vs 6%), headache (14% vs 9%), influenza (6% vs 2%), and urinary tract infection (9% vs 6%).

DRUG INTERACTIONS

- Strong inducers of CYP3A4 such as rifampin significantly reduce macitentan exposure. Concomitant use of OPSUMIT with strong CYP3A4 inducers should be avoided.
- Strong inhibitors of CYP3A4 like ketoconazole approximately double macitentan exposure. Many HIV drugs like ritonavir are strong inhibitors of CYP3A4. Avoid concomitant use of OPSUMIT with strong CYP3A4 inhibitors. Use other PAH treatment options when strong CYP3A4 inhibitors are needed as part of HIV treatment.

Please see Brief Summary of Prescribing Information, including BOXED WARNING for embryo-fetal toxicity, on adjacent pages.

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BRIEF SUMMARY

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

WARNING: EMBRYO-FETAL TOXICITY

- **Do not administer OPSUMIT to a pregnant female because it may cause fetal harm *[see Contraindications (Pregnancy), Warnings and Precautions (Embryo-fetal Toxicity), Use in Specific Populations (Pregnancy)]*.**
- **Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception *[see Use in Special Populations (Females and Males of Reproductive Potential)]*.**
- **For all female patients, OPSUMIT is available only through a restricted program called the OPSUMIT Risk Evaluation and Mitigation Strategy (REMS) *[see Warnings and Precautions (OPSUMIT REMS Program)]*.**

INDICATIONS AND USAGE

Pulmonary Arterial Hypertension

OPSUMIT® is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression. Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment). OPSUMIT also reduced hospitalization for PAH.

Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years. Patients were treated with OPSUMIT monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids. Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%).

CONTRAINDICATIONS

Pregnancy

OPSUMIT may cause fetal harm when administered to a pregnant woman. OPSUMIT is contraindicated in females who are pregnant. OPSUMIT was consistently shown to have teratogenic effects when administered to animals. If OPSUMIT is used during pregnancy, apprise the patient of the potential hazard to a fetus [see *Warnings and Precautions (Embryo-fetal Toxicity)* and *Use in Specific Populations (Pregnancy)*].

WARNINGS AND PRECAUTIONS

Embryo-fetal Toxicity

OPSUMIT may cause fetal harm when administered during pregnancy and is contraindicated for use in females who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, ensure use of acceptable contraceptive methods and obtain monthly pregnancy tests [see *Dosage and Administration section 2.2 in full Prescribing Information* and *Use in Specific Populations (Pregnancy, Females and Males of Reproductive Potential)*].

OPSUMIT is available for females through the OPSUMIT REMS Program, a restricted distribution program [see *Warnings and Precautions (OPSUMIT REMS Program)*].

OPSUMIT REMS Program

For all females, OPSUMIT is available only through a restricted program called the OPSUMIT REMS Program, because of the risk of embryo-fetal toxicity [see *Contraindications (Pregnancy), Warnings and Precautions (Embryo-fetal Toxicity),* and *Use in Specific Populations (Pregnancy, Females and Males of Reproductive Potential)*].

Notable requirements of the OPSUMIT REMS Program include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the OPSUMIT REMS Program prior to initiating OPSUMIT. Male patients are not enrolled in the REMS.
- Females of reproductive potential must comply with the pregnancy testing and contraception requirements [see *Use in Specific Populations (Females and Males of Reproductive Potential)*].
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive OPSUMIT.

Further information is available at www.OPSUMITREMS.com or 1-866-228-3546. Information on OPSUMIT certified pharmacies or wholesale distributors is available through Actelion Pathways at 1-866-228-3546.

Hepatotoxicity

Other ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. The incidence of elevated aminotransferases in the study of OPSUMIT in PAH is shown in Table 1.

Table 1: Incidence of Elevated Aminotransferases in the SERAPHIN Study

	OPSUMIT 10 mg (N=242)	Placebo (N=249)
>3 × ULN	3.4%	4.5%
>8 × ULN	2.1%	0.4%

In the placebo-controlled study of OPSUMIT, discontinuations for hepatic adverse events were 3.3% in the OPSUMIT 10 mg group vs. 1.6% for placebo. Obtain liver enzyme tests prior to initiation of OPSUMIT and repeat during treatment as clinically indicated.

Advise patients to report symptoms suggesting hepatic injury (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching). If clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2 × ULN, or by clinical symptoms of hepatotoxicity, discontinue OPSUMIT. Consider re-initiation of OPSUMIT when hepatic enzyme levels normalize in patients who have not experienced clinical symptoms of hepatotoxicity.

Hemoglobin Decrease

Decreases in hemoglobin concentration and hematocrit have occurred following administration of other ERAs and were observed in clinical studies with OPSUMIT. These decreases occurred early and stabilized thereafter. In the placebo-controlled study of OPSUMIT in PAH, OPSUMIT 10 mg caused a mean decrease in hemoglobin from baseline to up to 18 months of about 1.0 g/dL compared to no change in the placebo group. A decrease in hemoglobin to below 10.0 g/dL was reported in 8.7% of the OPSUMIT 10 mg group and in 3.4% of the placebo group. Decreases in hemoglobin seldom require transfusion. Initiation of OPSUMIT is not recommended in patients with severe anemia. Measure hemoglobin prior to initiation of treatment and repeat during treatment as clinically indicated [see *Adverse Reactions (Clinical Trial Experience)*].

Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)

Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue OPSUMIT.

Decreased Sperm Counts

Other ERAs have caused adverse effects on spermatogenesis. Counsel men about potential effects on fertility [see *Use in Specific Populations (Females and Males of Reproductive Potential) and Nonclinical Toxicology (Carcinogenesis, Mutagenesis, Impairment of Fertility)*].

ADVERSE REACTIONS

Clinically significant adverse reactions that appear in other sections of the labeling include:

- Embryo-fetal Toxicity [see *Warnings and Precautions (Embryo-fetal Toxicity)*]
- Hepatotoxicity [see *Warnings and Precautions (Hepatotoxicity)*]
- Decrease in Hemoglobin [see *Warnings and Precautions (Hemoglobin Decrease)*]

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in 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 clinical practice.

Safety data for OPSUMIT were obtained primarily from one placebo-controlled clinical study in 742 patients with PAH (SERAPHIN study). The exposure to OPSUMIT in this trial was up to 3.6 years with a median exposure of about 2 years (N=542 for 1 year; N=429 for 2 years; and N=98 for more than 3 years). The overall incidence of treatment discontinuations because of adverse events was similar across OPSUMIT 10 mg and placebo treatment groups (approximately 11%).

Table 2 presents adverse reactions more frequent on OPSUMIT than on placebo by ≥3%.

Table 2: Adverse Reactions

Adverse Reaction	OPSUMIT 10 mg (N=242)	Placebo (N=249)
Anemia	13%	3%
Nasopharyngitis/pharyngitis	20%	13%
Bronchitis	12%	6%
Headache	14%	9%
Influenza	6%	2%
Urinary tract infection	9%	6%

DRUG INTERACTIONS

Strong CYP3A4 Inducers

Strong inducers of CYP3A4 such as rifampin significantly reduce macitentan exposure. Concomitant use of OPSUMIT with strong CYP3A4 inducers should be avoided [see *Clinical Pharmacology (Pharmacokinetics)*].

Strong CYP3A4 Inhibitors

Concomitant use of strong CYP3A4 inhibitors like ketoconazole approximately double macitentan exposure. Many HIV drugs like ritonavir are strong inhibitors of CYP3A4. Avoid concomitant use of OPSUMIT with strong CYP3A4 inhibitors [see *Clinical Pharmacology (Pharmacokinetics)*]. Use other PAH treatment options when strong CYP3A4 inhibitors are needed as part of HIV treatment [see *Clinical Pharmacology (Pharmacokinetics)*].

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category X.

Risk Summary

OPSUMIT may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. Macitentan was teratogenic in rabbits and rats at all doses tested. A no-effect dose was not established in either species. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential hazard to a fetus [see *Contraindications (Pregnancy)*].

Animal Data

In both rabbits and rats, there were cardiovascular and mandibular arch fusion abnormalities. Administration of macitentan to female rats from late pregnancy through lactation caused reduced pup survival and impairment of the male fertility of the offspring at all dose levels tested.

Nursing Mothers

It is not known whether OPSUMIT is present in human milk. Macitentan and its metabolites were present in the milk of lactating rats. Because many drugs are present in human milk and because of the potential for serious adverse reactions from macitentan in nursing infants, nursing mothers should discontinue nursing or discontinue OPSUMIT.

Pediatric use

The safety and efficacy of OPSUMIT in children have not been established.

Geriatric use

Of the total number of subjects in the clinical study of OPSUMIT for PAH, 14% were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Females and Males of Reproductive Potential

Females

Pregnancy Testing: Female patients of reproductive potential must have a negative pregnancy test prior to starting treatment with OPSUMIT and monthly pregnancy tests during treatment with OPSUMIT. Advise patients to contact their health care provider if they become pregnant or suspect they may be pregnant. Perform a pregnancy test if pregnancy is suspected for any reason. For positive pregnancy tests, counsel patients on the potential risk to the fetus [see *Boxed Warning* and *Dosage and Administration section 2.2 in full Prescribing Information*].

Contraception: Female patients of reproductive potential must use acceptable methods of contraception during treatment with OPSUMIT and for 1 month after treatment with OPSUMIT. Patients may choose one highly effective form of contraception (intrauterine devices (IUD), contraceptive implants or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a partner's vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider trained in contraceptive counseling [see *Boxed Warning*].

Males

Testicular effects: Like other endothelin receptor antagonists, OPSUMIT may have an adverse effect on spermatogenesis [see *Warnings and Precautions (Decreased Sperm Counts)* and *Nonclinical Toxicology (Carcinogenesis, Mutagenesis, Impairment of Fertility*].

OVERDOSAGE

OPSUMIT has been administered as a single dose of up to and including 600 mg to healthy subjects (60 times the approved dosage). Adverse reactions of headache, nausea and vomiting were observed. In the event of an overdose, standard supportive measures should be taken, as required. Dialysis is unlikely to be effective because macitentan is highly protein-bound.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Special Populations

There are no clinically relevant effects of age, sex, or race on the pharmacokinetics of macitentan and its active metabolite.

Renal impairment: Exposure to macitentan and its active metabolite in patients with severe renal impairment (CrCl 15-29 mL/min) compared to healthy subjects was increased by 30% and 60%, respectively. This increase is not considered clinically relevant.

Hepatic impairment: Exposure to macitentan was decreased by 21%, 34%, and 6% and exposure to the active metabolite was decreased by 20%, 25%, and 25% in subjects with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, and C), respectively. This decrease is not considered clinically relevant.

OPSUMIT® (macitentan)

Drug Interactions

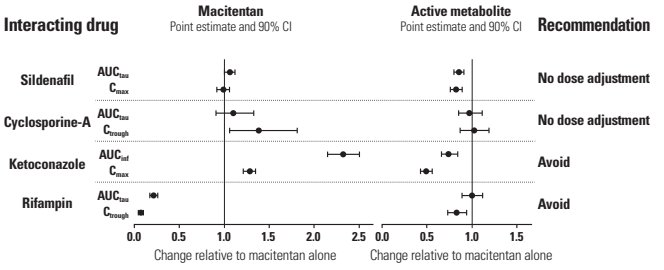
In vitro studies

At plasma levels obtained with dosing at 10 mg once daily, macitentan has no relevant inhibitory or inducing effects on CYP enzymes, and is neither a substrate nor an inhibitor of the multi-drug resistance protein (P-gp, MDR-1). Macitentan and its active metabolite are neither substrates nor inhibitors of the organic anion transporting polypeptides (OATP1B1 and OATP1B3) and do not significantly interact with proteins involved in hepatic bile salt transport, i.e., the bile salt export pump (BSEP) and the sodium-dependent taurocholate co-transporting polypeptide (NTCP).

In vivo studies

Effect of other drugs on macitentan: The effect of other drugs on macitentan and its active metabolite are studied in healthy subjects and are shown in Figure 1 below.

Figure 1



Effects of other strong CYP3A4 inhibitors such as ritonavir on macitentan were not studied, but are likely to result in an increase in macitentan exposure at steady state similar to that seen with ketoconazole [see *Drug Interactions (Strong CYP3A4 Inhibitors)*].

Effect of macitentan on other drugs

Warfarin: Macitentan once daily dosing did not alter the exposure to R- and S-warfarin or their effect on international normalized ratio (INR).

Sildenafil: At steady-state, the exposure to sildenafil 20 mg t.i.d. increased by 15% during concomitant administration of macitentan 10 mg once daily. This change is not considered clinically relevant.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies of 2 years' duration did not reveal any carcinogenic potential at exposures 75-fold and 140-fold the human exposure (based on AUC) in male and female mice, respectively, and 8.3- and 42-fold in male and female rats, respectively.

Mutagenesis: Macitentan was not genotoxic in a standard battery of *in vitro* and *in vivo* assays that included a bacterial reverse mutation assay, an assay for gene mutations in mouse lymphoma cells, a chromosome aberration test in human lymphocytes, and an *in vivo* micronucleus test in rats.

Impairment of Fertility: Treatment of juvenile rats from postnatal Day 4 to Day 114 led to reduced body weight gain and testicular tubular atrophy at exposures 7-fold the human exposure. Fertility was not affected.

Reversible testicular tubular dilatation was observed in chronic toxicity studies at exposures greater than 7-fold and 23-fold the human exposure in rats and dogs, respectively. After 2 years of treatment, tubular atrophy was seen in rats at 4-fold the human exposure. Macitentan did not affect male or female fertility at exposures ranging from 19- to 44-fold the human exposure, respectively, and had no effect on sperm count, motility, and morphology in male rats. No testicular findings were noted in mice after treatment up to 2 years.

Animal Toxicology

In dogs, macitentan decreased blood pressure at exposures similar to the therapeutic human exposure. Intimal thickening of coronary arteries was observed at 17-fold the human exposure after 4 to 39 weeks of treatment. Due to the species-specific sensitivity and the safety margin, this finding is considered not relevant for humans.

There were no adverse liver findings in long-term studies conducted in mice, rats, and dogs at exposures of 12- to 116-fold the human exposure.

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South San Francisco, CA 94080, USA
ACT20131018

Reference: 1. OPSUMIT full Prescribing Information. Actelion Pharmaceuticals US, Inc. October 2013.

ACTELION

Aspirin's benefits may be blunted in black women

BY BRUCE JANCIN
Frontline Medical News

CHICAGO – Postmenopausal African American women with subclinical atherosclerosis appear to be more resistant to the anti-inflammatory effects of daily aspirin than their white counterparts.

In a 6-month, double-blind, placebo-controlled pilot study, daily aspirin at 325 mg showed essentially no impact on high-sensitivity C-reactive protein (hsCRP) levels in the African American women. Moreover, their levels of interleukin-6 (IL-6) shot up while on aspirin. In contrast, levels of both proinflammatory markers declined markedly with aspirin therapy in the white women, Dr. Nora Alghothani reported at the joint meeting of the International Congress of Endocrinology and the Endocrine Society.

"Given apparent ethnic differences in response to aspirin-mediated anti-inflammatory benefits, perhaps a higher dose of aspirin may be required in African American women already at higher risk of inflammatory disease processes in order to reduce cardiovascular disease outcomes and lessen disparities," concluded Dr. Alghothani, of the department of endocrinology at the Ohio State University in Columbus.

This remark lit a four-alarm fire among audience members. They were quick to emphasize that aspirin at doses greater than 325 mg/day is associated with a sharply increased risk of bleeding and should thus not be considered as part of an individualized cardioprevention strategy for African American women unless and until there is solid evidence that the benefits outweigh the risks.

Dr. Alghothani concurred that a large-scale dose-response study is needed. In the meantime, though, the take home message of her pilot study is that physicians should not necessarily expect the same robust cardiovascular benefits with daily aspirin in their postmenopausal African American patients as in other populations, she added.

The pilot study included 42 postmenopausal, nondiabetic women with evidence of subclinical atherosclerosis based upon carotid intimal medial thickness measurements. Half were African American; half were white. Participants in each group were randomized in double-blind fashion to 6 months of aspirin at 325 mg/day or placebo, with fasting blood samples and anthropomorphic measurements obtained at baseline and 6 months. Consistent with findings from much larger studies, the African American women were heavier, with a mean body mass index of 32.8 kg/m^2, compared with 27.8 kg/m^2 for the white women. The African Americans also had significantly lower triglycerides and higher apolopoprotein A-I levels; however, the two groups didn't differ in terms of fasting insulin or glucose, high-density lipoprotein, low-density lipoprotein, or blood pressure.


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Postmenopausal black women may not have the same cardiovascular benefits with daily aspirin as white women do.

In the aspirin-treated African American women, levels of hsCRP remained static over time, going from a mean of 4.53 mg/L at baseline to 4.62 mg/L at 6 months. In placebo-treated African American women, however, hsCRP jumped from 3.34 mg/L at baseline to 8.36 mg/L at follow-up.

The mean hsCRP in white women on aspirin dropped from 2.13 to 1.6 mg/L over the course of 6 months, while with placebo it went from 2.19 to 2.69 mg/L.

Levels of IL-6 in aspirin-treated African American women climbed from 0.93 pg/mL at baseline to 2.56

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VIEW ON THE NEWS

Dr. Jennifer Cox, FCCP, comments: Although most results were not statistically significant, Dr. Alghothani presents an interesting pilot study that revealed the blunted response in anti-inflammatory markers to aspirin between African American women and white women. More studies are needed before changing prescribing practices, but it is clear that genetics, ethnicity, and drug metabolism should be on the forefront of drug research for more that just antineoplastic therapies.

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ICD-10: Dual coding is only for testing, backlog

BY MARY ELLEN SCHNEIDER
Frontline Medical News

There's plenty to be confused about when it comes to the transition to the new ICD-10 coding system in October 2015. But the government has issued some clarification about at least one issue: when to use dual coding.

Dual coding, also called dual processing, generally means using both ICD-9 and ICD-10 at the same time when submitting claims.

In an e-mail July 10, officials at the Centers for Medicare & Medicaid Services (CMS) said physicians and coders may engage in dual coding as a way to test their ICD-10 readiness before the compliance date. They may also code in both systems after the compliance date, if they have a backlog of claims.

Here's how it works: Before ICD-10 goes into effect on Oct. 1, 2015, physicians and coders can practice by coding current claims in both systems to see if they have the right level of documentation for the new system. ICD-10 codes can also be used to test whether payers and clearinghouses are ready to receive and process the new codes. However, only the ICD-9 code can be sent to payers as part of a "live" transaction before the compliance date.

Physicians may also find that they will use both coding sets for a short period of time after the compliance date, if they need to submit claims with a date of service that occurred before Oct. 1, 2015.

But the physicians and coders don't get to choose which system to code in. The date of service determines whether ICD-9 or ICD-10 is used, according to CMS, with services performed before Oct. 1 getting an ICD-9 code and services on and after Oct. 1 receiving an ICD-10 code. CMS is expected to release more details on the rollout of ICD-10 soon.

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Continued from previous page

pg/mL at 6 months. In contrast, mean IL-6 levels in white women on daily aspirin fell from 2.69 to 1.39 pg/mL. White women on placebo experienced a rise in IL-6 from 0.58 to 2.97 pg/mL.

Most of these differences didn't achieve statistical significance because of the small sample size, but the consistent trends suggest an overall blunted response to the anti-inflammatory effects of aspirin among African Americans, according to Dr. Alghothani. She added that these findings might help explain the well-documented ethnic disparities in cardiovascular outcomes, whereby African American women have a significantly higher cardiovascular mortality rate than white women despite on average having higher HDL and lower triglycerides.

Her study was funded by the university's Center for Women's Health. She reported no financial conflicts.

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ACP guideline supports OSA diagnosis via in-lab test

BY MARY ANN MOON
Frontline Medical News

Clinicians should recommend a sleep study using polysomnography for adults who have unexplained daytime sleepiness, according to a clinical practice guideline on diagnosing obstructive sleep apnea.

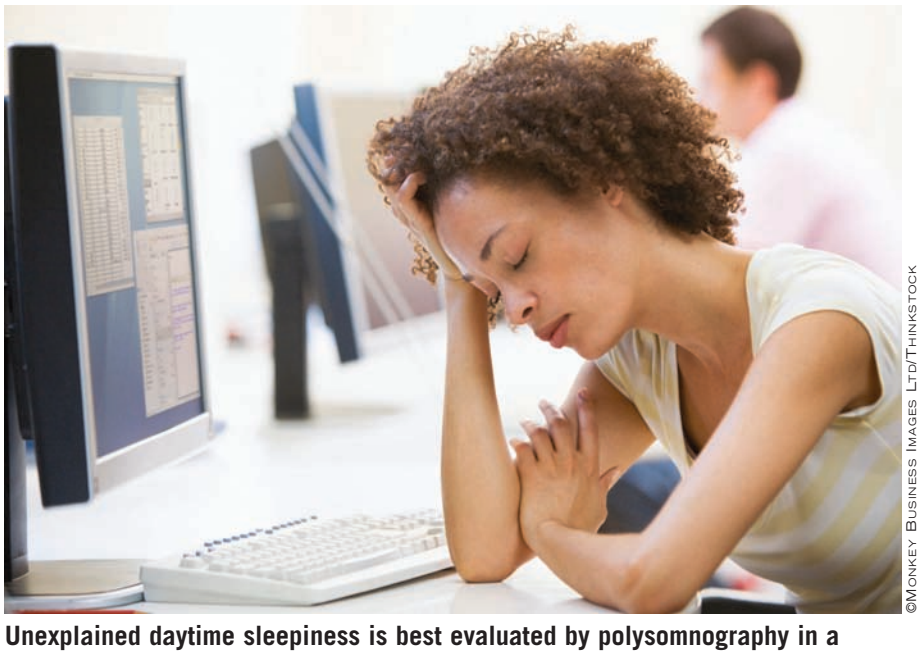
The guideline was in Annals of Internal Medicine.

There is still "considerable" controversy concerning the type and level of respiratory abnormality that defines obstructive sleep apnea (OSA), as well as the presence and type of signs or symptoms that are diagnostic of the disorder, said Dr. Amir Qaseem, director of clinical policy at the American College of Physicians, Philadelphia.

To formulate a clinical practice guideline, Dr. Qaseem and his associates performed a comprehensive review of the literature through May 2013, which included a comparative effectiveness technology review of portable sleep monitors sponsored by the Agency for Healthcare Research and Quality.

The guideline recommends that internists, family physicians, and other clinicians focus assessment of OSA on their adult patients who have unexplained daytime sleepiness. To do so, they must rule out other potential causes such as thyroid disease or gastroesophageal reflux disease.

Then, clinicians should evaluate patients for risk factors and common presenting symptoms of the disorder. Chief among risk factors is obesity, and frequent symptoms include unintentionally falling asleep during waking hours, unrefreshing sleep, fatigue, insomnia, and snoring (Ann. Intern. Med. 2014;161:210-20).



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Unexplained daytime sleepiness is best evaluated by polysomnography in a laboratory rather than via portable sleep monitors, the ACP recently stated.

Once OSA is suspected, the guideline recommends full-night, in-laboratory polysomnography to establish the diagnosis. This requires specialized facilities, is expensive, and demands that patients "spend the night under observation in a foreign environment," but yields the most accurate diagnostic information.

Portable sleep monitors for home use are an alternative if a sleep laboratory is not available, but these can yield substantially different scores on the apnea-hypopnea index, usually because of data loss that limits interpretation of the results.

In addition, the ability of portable sleep monitors to diagnose OSA is questionable in the subset of patients who have comorbid conditions such as chronic lung disease, heart failure, or neurologic disorders.

Development of this clinical practice guideline was supported solely by the American College of Physicians.

Dr. Qaseem and his associates reported no relevant financial conflicts of interest.

COMMENTARY: Home sleep tests have lower cost but less value

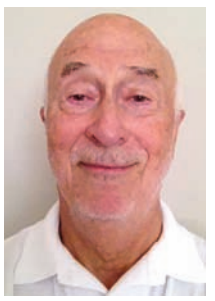
BY DR. MICHAEL L. COHEN, FCCP

A sleep physician, when presented with probable obstructive sleep apnea, needs to study the patient to confirm diagnosis, then treat the patient. The hard part is the treatment. The physician needs to convince people to accept continuous positive airway pressure (CPAP) therapy.

Dr. Charles W. Atwood, FCCP, associate professor of medicine at the University of Pittsburgh, recently reported that, in a controlled Veterans Affairs environment, over 2 years the cost of a home sleep test was $564 less than that of an in-lab study (CHEST Physician, June 2014 p. 27 [bit.ly/1qaxGpY]). It is no surprise that the tests cost less; however, he also stated that there was no difference in clinical outcomes after 2 years of follow-up.

I have practiced sleep medicine in a group of five physicians, all of whom are board certified in pulmonary disease and sleep medicine. Our studies are usually performed in an American Academy of Sleep Medicine–accredited eight-bed lab or a neighboring, accredited two-bed lab.

Whenever possible, we perform split-night studies on OSA patients. We utilize home sleep tests (HSTs) when appropriate, in accord with AASM guidelines. Our HST patients are taught how to wear the testing device, and if the study is positive, patients are given a 3-day trial of autotitrating CPAP, after a mask fitting, individual instructions, and the opportunity to call for help, 24/7.



DR. COHEN

On the other hand, we sometimes see HST devices that have been mailed to patients; and if the study is positive, a CPAP machine is mailed. We see patients who have had an HST ordered by a non–sleep physician, and the treatment is left to the durable medical equipment company. The physician seems to assume that the DME supplier will appropriately fit patient with mask and follow patient's compliance.

Unfortunately, this does not always happen. Patients may never be followed. Patients have appeared in our office, after 5 years of using CPAP, because they heard that there is a way to check compliance, or that they can get a new machine. Some patients' masks are held together with masking tape and superglue; and some patients have significant ulcerations on the bridge of their nose because of improper mask fit.

In our five-physician practice of sleep medicine, we use the equivalent of a full-time staff person to interact with the DME companies on the patient's behalf, and to correct problems with CPAP machines and masks.

Clearly, an HST without follow-up does not yield equivalent compliance compared with a lab split-night study. In the lab, the patient is introduced to CPAP by a compassionate sleep technologist, who is present during the titration to allay anxiety, to change masks as needed, and to reassure apprehensive patients. Without follow-up care, there is a much higher noncompliance rate.

Not only does the patient suffer when noncompliant with CPAP because of lack of adequate follow-up after an HST, but the bed partner's sleep is disturbed, families are disturbed by the patient's symptoms, job performance may suffer, and a sleepy driver is a potential danger to self and community. Payers may save dollars by paying for the HST per se; but without adequate follow-up of a patient after an HST, future health issues or accidents obviate any savings to the payer.

Conclusion: In a controlled setting, such as a Veterans Affairs hospital, where a sleep physician has control of testing, CPAP delivery, and follow-up, an HST may offer compliance similar to that of an in-lab study. However, in a community practice, even in a suburb where patients are well informed regarding their health issues, unless an HST is performed in a sleep center or by a physician knowledgeable in sleep medicine, who follows the patient and checks compliance, there is a major difference in the clinical success rate.

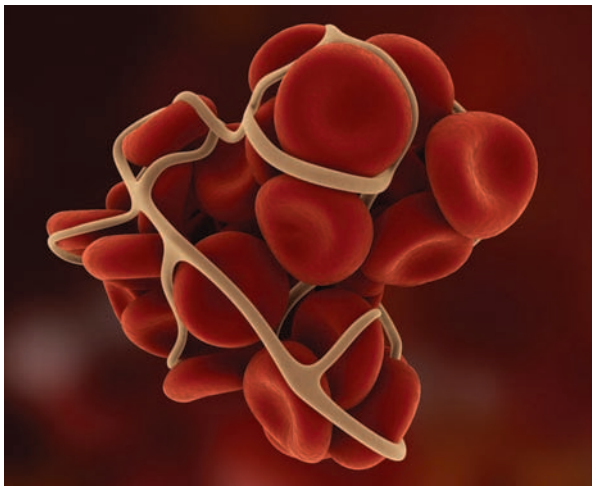
Without clinical follow-up of patient compliance, an HST per se may initially cost less, but the HST provides less value.

Dr. Cohen is a founding board member of the California Sleep Society and is in private practice in the San Francisco Bay area.

Anticoagulation alone is effective and safer

Thrombolysis *from page 1*

Conflicting data from several small studies as to the safety and effectiveness of catheter-directed thrombolysis have led professional societies to devise conflicting recommendations for its use: CHEST (the American College of Chest Physicians) advises against using the procedure, while the American Heart Association recommends it as a first-line therapy for certain patients. "We sought to assess real-world comparative-safety outcomes in patients with proximal and caval DVT who underwent catheter-directed thrombolysis plus anticoagulation with a group treated with anticoagulation alone using risk-adjusted propensity-score matching," the investigators said.



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Catheter-directed thrombolysis of DVT had higher risks of brain hemorrhage and pulmonary embolism.

They analyzed data from an Agency for Healthcare Research and Quality administrative database of patient discharges from approximately 1,000 nonfederal acute-care hospitals per year for a 6-year period. They identified 90,618 patients with a discharge diagnosis of proximal DVT; propensity-score matching yielded 3,594 well-matched patients in each study group. In-hospital mortality was not significantly different between patients who had catheter-directed thrombolysis plus anticoagulation (1.2%) and those who had anticoagulation alone (0.9%), Dr. Bashir and his associates said (JAMA Intern. Med. 2014 July 21 [doi:10.1001/jamainternmed.2014.3415]).

However, rates of blood transfusion (11.1% vs. 6.5%), pulmonary embolism (17.9% vs 11.4%), and intracranial hemorrhage (0.9% vs 0.3%) were significantly higher with the invasive intervention. And patients in the catheter-directed thrombolysis group required significantly longer hospitalizations (7.2 vs. 5.0 days) and incurred significantly higher hospital expenses ($85,094 vs. $28,164). "It is imperative that the magnitude of benefit from catheter-directed therapy be substantial to justify the increased initial resource utilization and bleeding risks of this therapy," the investigators noted.

VIEW ON THE NEWS

Dr. Steven Q. Simpson, FCCP, comments: This observational, real-world study provides more practical information, I believe, than we would obtain with a controlled trial for two drugs/techniques that are already FDA–approved for this purpose.We are able to infer how the drug/technique affects short-term mortality outcomes and financial costs beyond the strict selection criteria and adherence to a tight protocol that a trial requires. However, the study leaves us with the question of how catheter-directed thrombolysis compares with anticoagulation in the more immediately life-threatening setting of massive pulmonary embolism. Additionally, proponents of catheter-directed thrombolysis suggest that it reduces the pain and suffering of postphlebitic syndrome, an outcome not addressed by this study.

Regional variation seen in minimally invasive surgery

Quality *from page 1*

and hysterectomy. The researchers used a propensity score model to calculate the predicted proportion of minimally invasive operations for each hospital based on patient characteristics. For each procedure, they categorized hospitals as low, medium, or high based on their actual to predicted proportion of minimally invasive surgery use (BMJ 2014;349:g4198).

On average, the use of minimally invasive surgery by the hospitals sampled was 71% for appendectomy, 28% for colectomy, 13% for hysterectomy, and 32% for lung lobectomy. Overall surgical complications for minimally invasive surgery, compared with open surgery, were, respectively, for lung lobectomy: 17.1% vs. 25.4%; appendectomy: 3.94% vs. 7.90%; colectomy: 13.8% vs. 35.8%; and hysterectomy: 4.69% vs. 6.64%;. All differences were significant.

"In our analysis using Agency for Healthcare Research and Quality patient safety indicators for surgical care, we noted fewer wound, infectious, thrombotic, pulmonary, and mortality complications associated with minimally invasive surgery," the researchers wrote. "Based on our findings, increased hospital utilization of minimally invasive surgery at many U.S. hospitals represents a tremendous opportunity to prevent surgical site infection events."

The use of minimally invasive surgery was highly variable among the sampled hospitals. In fact, some never used minimally invasive surgery for some of the four procedures, while others used minimally invasive surgery for more than 75% of these procedures. Factors associated with the use of minimally invasive surgery were urban location, large hospital size, teaching hospital, and, for certain procedures, the hospital being located in the Midwest, South, or West.

"This [regional] disparity may be due to the broad range of surgical services some surgeons in rural areas are required to provide, and a scarcity of surgical specialists in such areas with advanced skills in minimally invasive surgery. Alternatively, the disparity may be a function of a lack of patient awareness about surgical options, decreased competition for patients, or a lack of minimally invasive surgery equipment, staff, or support in rural areas," the researchers wrote.

The findings of underutilization of minimally invasive surgery may also have to do with a training gap.

"One reason that hospitals may be underperforming minimally invasive surgery is variability in appropriate training in residency and fellowship," Dr. Makary and his associates wrote. "One strategy that hospitals may consider in managing surgeons who cannot or choose not to acquire skills for performing minimally invasive surgery is to create a division of labor where patients who are not candidates for minimally invasive surgery are cared for by these surgeons. Increased standardization of competencies in minimally invasive surgery in surgical residency is needed to tackle wide variations in training."

The researchers acknowledged certain limitations of the study, including the fact that administrative claims data "can have incomplete coding, particularly of preexisting conditions," they wrote. "Another limitation is the lack of information available in the database for physician factors, such as laparoscopic training and experience that may influence the choice of procedure."

The researchers stated that they had no relevant financial conflicts to disclose.

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VIEW ON THE NEWS

Dr. Frank Podbielski, FCCP, comments: The data presented show that regional differences exist in the United States for the application of certain minimally invasive surgical procedures. The study does not control for patient selection, thus a direct comparison of infection and complication rates between open and minimally invasive procedures is not supported.

Additionally, findings of this study raise troubling questions regarding overspecialization of training programs such that residents are taught to perform specific operations rather than to learn general surgical techniques that are applicable across the entire spectrum of operative care.

For your patients with chronic obstructive pulmonary disease (COPD) who require maintenance bronchodilator treatment

Help Your Patients Breathe Better With ANORO ELLIPTA

Indication

- ANORO ELLIPTA is a combination anticholinergic/long-acting beta$_2$-adrenergic agonist indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.
- ANORO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

Important Safety Information for ANORO ELLIPTA

WARNING: ASTHMA-RELATED DEATH

- **Long-acting beta$_2$-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABA, including vilanterol.**
- **The safety and efficacy of ANORO ELLIPTA in patients with asthma have not been established. ANORO ELLIPTA is not indicated for the treatment of asthma.**

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- ANORO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.
- ANORO ELLIPTA should not be used for the relief of acute symptoms, ie, as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist.
- ANORO ELLIPTA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using ANORO ELLIPTA should not use another medicine containing a LABA (eg, salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
- Caution should be exercised when considering the coadministration of ANORO ELLIPTA with long-term ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue ANORO ELLIPTA and institute alternative therapy.
- Vilanterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms. If such effects occur, ANORO ELLIPTA may need to be discontinued. ANORO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

ANORO ELLIPTA significantly improved trough (predose) FEV_1 by 167 mL vs placebo ($P<0.001$) at Day 169[1]

A 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study compared the efficacy and safety of ANORO ELLIPTA (n=413) and placebo (n=280), each administered once daily by the ELLIPTA inhaler. The primary endpoint was trough (predose) FEV_1 at Day 169 (defined as the mean of the FEV_1 values obtained 23 and 24 hours after dosing on Day 168).[1]

Once-daily ANORO ELLIPTA

The first and only FDA-approved product for patients with COPD combining 2 long-acting bronchodilators in 1 inhaler

Important Safety Information for ANORO ELLIPTA (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Use with caution in patients with narrow-angle glaucoma. Instruct patients to contact a physician immediately if signs or symptoms of acute narrow-angle glaucoma develop.
- Use with caution in patients with urinary retention, especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to contact a physician immediately if signs or symptoms of urinary retention develop.
- Be alert to hypokalemia and hyperglycemia.

ADVERSE REACTIONS

- The most common adverse reactions (≥1% and more common than placebo) reported in four 6-month clinical trials with ANORO ELLIPTA (and placebo) were: pharyngitis, 2% (<1%); sinusitis, 1% (<1%); lower respiratory tract infection, 1% (<1%); constipation, 1% (<1%); diarrhea, 2% (1%); pain in extremity, 2% (1%); muscle spasms, 1% (<1%); neck pain, 1% (<1%); and chest pain, 1% (<1%).
- In addition to the 6-month efficacy trials with ANORO ELLIPTA, a 12-month trial evaluated the safety of umeclidinium/vilanterol 125 mcg/25 mcg in subjects with COPD. Adverse reactions (incidence ≥1% and more common than placebo) in subjects receiving umeclidinium/vilanterol 125 mcg/25 mcg were: headache, back pain, sinusitis, cough, urinary tract infection, arthralgia, nausea, vertigo, abdominal pain, pleuritic pain, viral respiratory tract infection, toothache, and diabetes mellitus.

DRUG INTERACTIONS

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

Reference: 1. Donohue JF, Maleki-Yazdi MR, Kilbride S, et al. Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD. *Respir Med.* 2013;107(10):1538-1546.

Please see Brief Summary of Prescribing Information, including Boxed Warning, for ANORO ELLIPTA on the following pages.

ANORO ELLIPTA was developed in collaboration with Theravance

ANORO™ ELLIPTA™
(umeclidinium 62.5 mcg and vilanterol 25 mcg inhalation powder)

BRIEF SUMMARY

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

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABA, including vilanterol, one of the active ingredients in ANORO ELLIPTA *[see Warnings and Precautions (5.1)]*.

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

1 INDICATIONS AND USAGE
ANORO ELLIPTA is a combination anticholinergic/long-acting beta$_2$-adrenergic agonist (anticholinergic/LABA) indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.
Important Limitations of Use: ANORO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

4 CONTRAINDICATIONS
The use of ANORO ELLIPTA is contraindicated in patients with severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to umeclidinium, vilanterol, or any of the excipients *[see Warnings and Precautions (5.6), Description (11) of full Prescribing Information]*.

5 WARNINGS AND PRECAUTIONS
5.1 Asthma-Related Death
- Data from a large placebo-controlled trial in subjects with asthma showed that LABA may increase the risk of asthma-related death. Data are not available to determine whether the rate of death in patients with COPD is increased by LABA.
- A 28-week, placebo-controlled, US trial comparing the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs. 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). The increased risk of asthma-related death is considered a class effect of LABA, including vilanterol, one of the active ingredients in ANORO ELLIPTA.
- No trial adequate to determine whether the rate of asthma-related death is increased in subjects treated with ANORO ELLIPTA has been conducted. The safety and efficacy of ANORO ELLIPTA in patients with asthma have not been established. ANORO ELLIPTA is not indicated for the treatment of asthma.

5.2 Deterioration of Disease and Acute Episodes
ANORO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD. ANORO ELLIPTA has not been studied in subjects with acutely deteriorating COPD. The initiation of ANORO ELLIPTA in this setting is not appropriate.
ANORO ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. ANORO ELLIPTA has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist. When beginning treatment with ANORO ELLIPTA, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms. When prescribing ANORO ELLIPTA, the healthcare provider should also prescribe an inhaled, short-acting beta$_2$-agonist and instruct the patient on how it should be used. Increasing inhaled, short-acting beta$_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.
COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If ANORO ELLIPTA no longer controls symptoms of bronchoconstriction; the patient's inhaled, short-acting, beta$_2$-agonist becomes less effective; or the patient needs more short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of ANORO ELLIPTA beyond the recommended dose is not appropriate in this situation.
5.3 Excessive Use of ANORO ELLIPTA and Use With Other Long-Acting Beta$_2$-Agonists
ANORO ELLIPTA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using ANORO ELLIPTA should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
5.4 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors
Caution should be exercised when considering the coadministration of ANORO ELLIPTA with long-term ketoconazole and other known strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full Prescribing Information]*.
5.5 Paradoxical Bronchospasm
As with other inhaled medicines, ANORO ELLIPTA can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with ANORO ELLIPTA, it should be treated immediately with an inhaled, short-acting bronchodilator; ANORO ELLIPTA should be discontinued immediately; and alternative therapy should be instituted.
5.6 Hypersensitivity Reactions
Hypersensitivity reactions may occur after administration of ANORO ELLIPTA. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder products containing lactose; therefore, patients with severe milk protein allergy should not use ANORO ELLIPTA *[see Contraindications (4)]*.
5.7 Cardiovascular Effects
Vilanterol, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms *[see Clinical Pharmacology (12.2) of full Prescribing Information]*. If such effects occur, ANORO ELLIPTA may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown.
Therefore, ANORO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
5.8 Coexisting Conditions
ANORO ELLIPTA, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.
5.9 Worsening of Narrow-Angle Glaucoma
ANORO ELLIPTA should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.
5.10 Worsening of Urinary Retention
ANORO ELLIPTA should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.
5.11 Hypokalemia and Hyperglycemia
Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medicines may produce transient hyperglycemia in some patients. In 4 clinical trials of 6-month duration evaluating ANORO ELLIPTA in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

6 ADVERSE REACTIONS
LABA, such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. ANORO ELLIPTA is not indicated for the treatment of asthma. *[See Boxed Warning and Warnings and Precautions (5.1).]*
The following adverse reactions are described in greater detail in other sections:
- Paradoxical bronchospasm *[see Warnings and Precautions (5.5)]*
- Cardiovascular effects *[see Warnings and Precautions (5.7)]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.9)]*
- Worsening of urinary retention *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.
The clinical program for ANORO ELLIPTA included 8,138 subjects with COPD in four 6-month lung function trials, one 12-month long-term safety study, and 9 other trials of shorter duration. A total of 1,124 subjects have received at least 1 dose of ANORO ELLIPTA (umeclidinium/vilanterol 62.5 mcg/25 mcg), and 1,330 subjects have received a higher dose of umeclidinium/vilanterol (125 mcg/25 mcg). The safety data described below are based on the four 6-month and the one 12-month trials. Adverse reactions observed in the other trials were similar to those observed in the confirmatory trials.
6-Month Trials: The incidence of adverse reactions associated with ANORO ELLIPTA in Table 1 is based on four 6-month trials: 2 placebo-controlled trials (Trials 1 and 2; n = 1,532 and n = 1,489, respectively) and 2 active-controlled trials (Trials 3 and 4; n = 843 and n = 869, respectively). Of the 4,733 subjects, 68% were male and 84% were Caucasian. They had a mean age of 63 years and an average smoking history of 45 pack-years, with 50% identified as current smokers. At screening, the mean post-bronchodilator percent predicted forced expiratory volume in 1 second (FEV_1) was 48% (range: 13% to 76%), the mean post-bronchodilator FEV_1/forced vital capacity (FVC) ratio was 0.47 (range: 0.13 to 0.78), and the mean percent reversibility was 14% (range: -45% to 109%). Subjects received 1 dose once daily of the following: ANORO ELLIPTA, umeclidinium/vilanterol 125 mcg/25 mcg, umeclidinium 62.5 mcg, umeclidinium 125 mcg, vilanterol 25 mcg, active control, or placebo.

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

Adverse Reaction	Placebo (n = 555) %	ANORO ELLIPTA (n = 842) %	Umeclidinium 62.5 mcg (n = 418) %	Vilanterol 25 mcg (n = 1,034) %
Infections and infestations				
Pharyngitis	<1	2	1	2
Sinusitis	<1	1	<1	1
Lower respiratory tract infection	<1	1	<1	<1
Gastrointestinal disorders				
Constipation	<1	1	<1	<1
Diarrhea	1	2	<1	2
Musculoskeletal and connective tissue disorders				
Pain in extremity	1	2	<1	2
Muscle spasms	<1	1	<1	<1
Neck pain	<1	1	<1	<1
General disorders and administration site conditions				
Chest pain	<1	1	<1	<1

Other adverse reactions with ANORO ELLIPTA observed with an incidence less than 1% but more common than with placebo included the following: productive cough, dry mouth, dyspepsia, abdominal pain, gastroesophageal reflux disease, vomiting, musculoskeletal chest pain, chest discomfort, asthenia, atrial fibrillation, ventricular extrasystoles, supraventricular extrasystoles, myocardial infarction, pruritus, rash, and conjunctivitis.
12-Month Trial: In a long-term safety trial, 335 subjects were treated for up to 12 months with umeclidinium/vilanterol 125 mcg/25 mcg or placebo. The demographic and baseline characteristics of the long-term safety trial were similar to those of the placebo-controlled efficacy trials described above. Adverse reactions that occurred with a frequency of greater than or equal to 1% in the group receiving umeclidinium/vilanterol 125 mcg/25 mcg that exceeded that in placebo in this trial were: headache, back pain, sinusitis, cough, urinary tract infection, arthralgia, nausea, vertigo, abdominal pain, pleuritic pain, viral respiratory tract infection, toothache, and diabetes mellitus.

7 DRUG INTERACTIONS
7.1 Inhibitors of Cytochrome P450 3A4
Vilanterol, a component of ANORO ELLIPTA, is a substrate of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to vilanterol. Caution should be exercised when

considering the coadministration of ANORO ELLIPTA with ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) *[see Warnings and Precautions (5.4), Clinical Pharmacology (12.3) of full Prescribing Information]*.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

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

7.3 Beta-Adrenergic Receptor Blocking Agents

Beta-blockers not only block the pulmonary effect of beta-agonists, such as vilanterol, a component of ANORO ELLIPTA, but may produce severe bronchospasm in patients with COPD. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

7.4 Non–Potassium-Sparing Diuretics

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

7.5 Anticholinergics

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

Umeclidinium: There was no evidence of teratogenic effects in rats and rabbits at approximately 50 and 200 times, respectively, the MRHDID (maximum recommended human daily inhaled dose) in adults (on an AUC basis at maternal inhaled doses up to 278 mcg/kg/day in rats and at maternal subcutaneous doses up to 180 mcg/kg/day in rabbits).

Vilanterol: There were no teratogenic effects in rats and rabbits at approximately 13,000 and 70 times, respectively, the MRHDID in adults (on a mcg/m^2 basis at maternal inhaled doses up to 33,700 mcg/kg/day in rats and on an AUC basis at maternal inhaled doses up to 591 mcg/kg/day in rabbits). However, fetal skeletal variations were observed in rabbits at approximately 450 times the MRHDID in adults (on an AUC basis at maternal inhaled or subcutaneous doses of 5,740 or 300 mcg/kg/day, respectively). The skeletal variations included decreased or absent ossification in cervical vertebral centrum and metacarpals.

Nonteratogenic Effects: *Umeclidinium:* There were no effects on perinatal and postnatal developments in rats at approximately 80 times the MRHDID in adults (on an AUC basis at maternal subcutaneous doses up to 180 mcg/kg/day).

Vilanterol: There were no effects on perinatal and postnatal developments in rats at approximately 3,900 times the MRHDID in adults (on a mcg/m^2 basis at maternal oral doses up to 10,000 mcg/kg/day).

8.2 Labor and Delivery

There are no adequate and well-controlled human trials that have investigated the effects of ANORO ELLIPTA during labor and delivery.

Because beta-agonists may potentially interfere with uterine contractility, ANORO ELLIPTA should be used during labor only if the potential benefit justifies the potential risk.

8.3 Nursing Mothers

ANORO ELLIPTA: It is not known whether ANORO ELLIPTA is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when ANORO ELLIPTA is administered to a nursing woman. Since there are no data from well-controlled human studies on the use of ANORO ELLIPTA by nursing mothers, based on the data for the individual components, a decision should be made whether to discontinue nursing or to discontinue ANORO ELLIPTA, taking into account the importance of ANORO ELLIPTA to the mother.

Umeclidinium: It is not known whether umeclidinium is excreted in human breast milk. However, administration to lactating rats at approximately 25 times the MRHDID in adults resulted in a quantifiable level of umeclidinium in 2 pups, which may indicate transfer of umeclidinium in milk.

Vilanterol: It is not known whether vilanterol is excreted in human breast milk. However, other beta$_2$-agonists have been detected in human milk.

8.4 Pediatric Use

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

8.5 Geriatric Use

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

Clinical trials of ANORO ELLIPTA for COPD included 2,143 subjects aged 65 and older and, of those, 478 subjects were aged 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

8.6 Hepatic Impairment

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

8.7 Renal Impairment

There were no significant increases in either umeclidinium or vilanterol exposure in subjects with severe renal impairment (CrCl<30 mL/min) compared with healthy subjects. No dosage adjustment is required in patients with renal impairment *[see Clinical Pharmacology (12.3) of full Prescribing Information]*.

10 OVERDOSAGE

No case of overdose has been reported with ANORO ELLIPTA.

ANORO ELLIPTA contains both umeclidinium and vilanterol; therefore, the risks associated with overdosage for the individual components described below apply to ANORO ELLIPTA. Treatment of overdosage consists of discontinuation of ANORO ELLIPTA together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medicine can produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage.

10.1 Umeclidinium

High doses of umeclidinium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a once-daily inhaled dose of up to 1,000 mcg umeclidinium (16 times the maximum recommended daily dose) for 14 days in subjects with COPD.

10.2 Vilanterol

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

ANORO ELLIPTA: No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with ANORO ELLIPTA; however, studies are available for individual components, umeclidinium and vilanterol, as described below.

Umeclidinium: Umeclidinium produced no treatment-related increases in the incidence of tumors in 2-year inhalation studies in rats and mice at inhaled doses up to 137 mcg/kg/day and 295/200 mcg/kg/day (male/female), respectively (approximately 20 and 25/20 times the MRHDID in adults on an AUC basis, respectively).

Umeclidinium tested negative in the following genotoxicity assays: the *in vitro* Ames assay, *in vitro* mouse lymphoma assay, and *in vivo* rat bone marrow micronucleus assay.

No evidence of impairment of fertility was observed in male and female rats at subcutaneous doses up to 180 mcg/kg/day and inhaled doses up to 294 mcg/kg/day, respectively (approximately 100 and 50 times, respectively, the MRHDID in adults on an AUC basis).

Vilanterol: In a 2-year carcinogenicity study in mice, vilanterol caused a statistically significant increase in ovarian tubulostromal adenomas in females at an inhalation dose of 29,500 mcg/kg/day (approximately 7,800 times the MRHDID in adults on an AUC basis). No increase in tumors was seen at an inhalation dose of 615 mcg/kg/day (approximately 210 times the MRHDID in adults on an AUC basis).

In a 2-year carcinogenicity study in rats, vilanterol caused statistically significant increases in mesovarian leiomyomas in females and shortening of the latency of pituitary tumors at inhalation doses greater than or equal to 84.4 mcg/kg/day (greater than or equal to approximately 20 times the MRHDID in adults on an AUC basis). No tumors were seen at an inhalation dose of 10.5 mcg/kg/day (approximately 1 time the MRHDID in adults on an AUC basis).

These tumor findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Vilanterol tested negative in the following genotoxicity assays: the *in vitro* Ames assay, *in vivo* rat bone marrow micronucleus assay, *in vivo* rat unscheduled DNA synthesis (UDS) assay, and *in vitro* Syrian hamster embryo (SHE) cell assay. Vilanterol tested equivocal in the *in vitro* mouse lymphoma assay.

No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at inhaled vilanterol doses up to 31,500 and 37,100 mcg/kg/day, respectively (approximately 12,000 and 14,500 times, respectively, the MRHDID in adults on a mcg/m^2 basis).

17 PATIENT COUNSELING INFORMATION

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

Asthma-Related Death: Inform patients that LABA, such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. ANORO ELLIPTA is not indicated for the treatment of asthma.

Not for Acute Symptoms: Inform patients that ANORO ELLIPTA is not meant to relieve acute symptoms of COPD and extra doses should not be used for that purpose. Advise them to treat acute symptoms with a rescue inhaler such as albuterol. Provide patients with such medicine and instruct them in how it should be used.

Instruct patients to seek medical attention immediately if they experience any of the following:

- Symptoms get worse
- Need for more inhalations than usual of their rescue inhaler

Patients should not stop therapy with ANORO ELLIPTA without physician/provider guidance since symptoms may recur after discontinuation.

Do Not Use Additional Long-Acting Beta$_2$-Agonists: Instruct patients to not use other medicines containing a LABA. Patients should not use more than the recommended once-daily dose of ANORO ELLIPTA.

Instruct patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis to discontinue the regular use of these products and use them only for the symptomatic relief of acute symptoms.

Paradoxical Bronchospasm: As with other inhaled medicines, ANORO ELLIPTA can cause paradoxical bronchospasm. If paradoxical bronchospasm occurs, instruct patients to discontinue ANORO ELLIPTA.

Risks Associated With Beta-Agonist Therapy: Inform patients of adverse effects associated with beta$_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

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

Worsening of Urinary Retention: Instruct patients to be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

ANORO ELLIPTA was developed in collaboration with Theravance.

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COMMENTARY: Evidence base is still missing in bronchiolitis care

BY DR. SUSAN MILLARD, FCCP

A recent study titled "Racial/Ethnic differences in the presentation and management of severe bronchiolitis" investigates the multiple factors related to the presentation and management of bronchiolitis in the United States and hypothesizes that there are disparities among ethnic groups.

The study expands on concerns that the 2006 Academy of Pediatrics Bronchiolitis guidelines are not being followed (Pediatrics 2006;118:1774-93). The study brings up important topics for practitioners, epidemiologists, and insurance companies. Jonathan Santiago, M.P.H., and his colleagues at Yale University, New Haven, Conn., conclude that non-Hispanic black children were more likely to receive albuterol before admission and less likely to receive chest radiographs during hospitalization while Hispanic children are most likely to be discharged on inhaled corticosteroids.

However, it is important to review the study to understand the potential implications:

The study by Mr. Santiago, a medical student at Yale, and his colleagues has significant flaws with the inclusion and exclusion criteria. These flaws could have significantly affected the authors' conclusions. Still, the research highlights important issues: "Why are clinicians not following the guidelines for all our U.S. infants and toddlers?" And, "Why do clinicians not use evidence-based medicine?" If clinicians are treating young children from ethnic groups differently, why is that happening?

DR. MILLARD

The AAP guidelines were developed with the support of the American Academy of Family Physicians, the American College of Chest Physicians (CHEST), the American Thoracic Society, and the European Respiratory Society. The guidelines outline that clinicians should diagnose bronchiolitis and assess severity based on a standard history and physical. Chest radiographs should not be routinely ordered. The guidelines also recommend that a carefully monitored trial of alpha-adrenergic or beta-adrenergic medication is an option. However, inhaled bronchodilators should be continued only if there is a documented positive response. Among many other recommendations, corticosteroids are definitively not recommended for routine bronchiolitis treatment.

The Journal of Pediatrics recently published an article by Dr. Todd A. Florin of the Cincinnati Children's Hospital and his colleagues on variation in the management of hospitalized infants with bronchiolitis (2014;pii: S0022-3476[14]00507-1 [doi:10.1016/j.jpeds.2014.05.057]). More than 60,000 hospitalizations were analyzed for infants aged 12 months and younger. After adjustment for patient characteristics, obtaining a chest radiograph was the one factor that had a great variation between hospitals. There was an 8.6% decrease in obtaining chest x-rays during the study period of 2007-2012. There also was wide variation among hospitals in regard to bronchodilator use, and there was no decrease in its use observed over the study period, despite the guidelines. Finally, a decrease of only 3.3% in corticosteroid use occurred during 2007-2012 – after the guidelines came out!

There is a theme: Family physicians, pediatricians, and other health care providers are not assessing and managing bronchiolitis using evidence-based medicine.

Mr. Santiago's multicenter trial looked at 2,130 subjects; 24% were non-Hispanic blacks and 38% were Hispanic. Their median age was 4 months, while the mean age of the children in Dr. Florin's study was 3.7 months. Many points of these studies can be teased out. For example, in Mr. Santiago's study, non-Hispanic black children were more likely to receive albuterol before admission with an odds ratio of 1.58, and in the larger study by Dr. Florin, use of albuterol, in general, increased the patients' length of stay. If Mr. Santiago's study were expanded with stricter entry criteria and more hospitals, would a similar increased length of stay be found among non-Hispanic black children?

The guidelines are now 8 years old, and new guidelines are coming. But this important information, thoroughly analyzed by respected thought leaders, should be well disseminated among our peers.

Our common goal should be to make sure that children at risk are not subjected to unnecessary x-rays, breathing treatments, and medications for bronchiolitis. The Hippocratic Oath, loosely translated, states: "I will prescribe regimens for the good of my patients according to my ability and my judgment and never do harm to anyone."

Dr. Millard is a pediatric pulmonologist and director of the pediatric pulmonary diagnostics laboratory at Helen DeVos Children's Hospital in Grand Rapids, Mich.

3% hypertonic saline fails to boost bronchiolitis outcomes

BY SHARON WORCESTER

Frontline Medical News

LAKE BUENA VISTA, FLA. – The median length of stay and rate of readmission did not differ between infants with bronchiolitis who were treated with nebulized 3% hypertonic saline and those treated with normal saline in the first U.S. prospective, double-blind, randomized controlled trial comparing the two treatments.

The median length of stay was 2.0 days in 93 infants younger than age 12 months who were admitted to an urban tertiary care children's hospital with a diagnosis of bronchiolitis and who were randomized to receive the hypertonic saline treatments without concomitant bronchodilators, and 2.0 days in 97 such infants who received normal saline without bronchodilators, Dr. Alyssa Silver reported at the Pediatric Hospital Medicine 2014 meeting.

The mean length of stay also did not differ significantly between the groups, nor did the rate of readmission and rate of adverse event, Dr. Silver, a pediatric hospitalist and director of pediatric inpatient physician assistant services at the Children's Hospital at Montefiore, Bronx, N.Y., reported at the meeting, which was sponsored by the Society of Hospital Medicine, the American Academy of Pediatrics, the AAP Section on Hospital Medicine, and the Academic Pediatric Association.

Infants offered enrollment were those admitted with bronchiolitis to an urban tertiary care children's hospital in a population with a high endemic prevalence of asthma. Those with status asthmaticus, certain chronic diseases, and prior exposure to hypertonic saline were among those excluded.

The infants included in the study were enrolled within 12 hours of admission between 2011 and 2014, received 4 mL of hypertonic or normal saline every 4 hours via standard hospital wall nebulizer until discharge and were assessed daily by study personnel who made follow-up calls at 1 week and 1 month after discharge to document readmissions.

To address the theoretical concern of bronchospasm with hypertonic saline, researchers evaluated patients using the Respiratory Distress Assessment Instrument prior to first study treatment and at 30 minutes after the treatment as a safety measure; patients were withdrawn if the measure increased by four or more points, Dr. Silver said.

The treatment and control groups were similar with respect to demographic factors.

Subgroup analyses showed no differences in length of stay between infants in the treatment and control groups who were respiratory syncytial virus positive, had a history of wheezing, or had a history of prematurity, Dr. Silver noted.

Enrollment in the study was halted at the time of an interim analysis because of the lack of difference in length of stay between the groups.

Bronchiolitis is the leading cause of hospitalization for children under 12 months of age – at a cost of about $500 million each year. The national average length of stay for infants with bronchiolitis is 3.3 days.

"Despite the high incidence of bronchiolitis, there is a lack of a unified inpatient treatment plan beyond supportive care of oxygen and intravenous hydration. Many different approaches have been used, but none have proven useful," Dr. Silver said, adding that interest in the use of nebulized hypertonic saline has been on the rise.

The study was limited by the single-center design, and lack of complete coverage for recruiting of admitted patients (the study was unfunded and relied on voluntary study personnel), although more than 75% of patients admitted for bronchiolitis were offered enrollment.

Dr. Silver reported having no disclosures.

Thoracic radiotherapy backed for extensive SCLC

BY PATRICE WENDLING
Frontline Medical News

CHICAGO – Thoracic radiotherapy improved overall survival, progression-free survival, and intrathoracic control in patients with extensive small-cell lung cancer who responded to chemotherapy, according to results from the randomized CREST study.

"Thoracic radiotherapy should be offered in addition to PCI [prophylactic cranial irradiation] to all extensive-stage small-cell lung cancer patients responding to initial chemotherapy," Dr. Ben J. Slotman said at the annual meeting of the American Society of Clinical Oncology.

The rationale for CREST (Chest Radiotherapy Extensive Stage Trial) was based on an earlier trial by Dr. Slotman showing that prophylactic cranial irradiation not only lowered the risk of symptomatic brain metastases but also significantly improved 1-year overall survival compared with no additional therapy in patients with extensive small-cell lung cancer (SCLC) who had any response to chemotherapy (N. Engl. J. Med. 2007;357:664-72).

Most patients, however, had persistent intrathoracic disease after chemotherapy or intrathoracic progression, said Dr. Slotman, professor and head of radiation oncology, VU Medical Center, Amsterdam.

CREST investigators at 42 centers in the Netherlands, the United Kingdom, Norway, and Belgium randomly assigned 498 patients with any response after four to six cycles of initial platinum-based chemotherapy to thoracic radiotherapy (TRT) (30 Gy in 10 fractions) plus PCI or PCI only. Treatment began within 2-7 weeks of their last chemotherapy. Patients with brain or plural metastasis, pleuritis carcinomatosa, or prior radiotherapy (RT) to the brain or thorax were excluded.

About 70% of patients had a partial response to chemotherapy, and also not reached, with 13 events in the placebo arm and 22 in the erlotinib arm (HR, 1.09; P = .81).

CREST *continued on following page*

VITALS

Key clinical point: Thoracic radiotherapy may improve survival when delivered after chemotherapy in extensive-stage lung cancer responding to chemotherapy.

Major finding: Overall survival at 1 year was not statistically different between the TRT and no TRT arms (HR, 0.84; P = .066) but was significantly different at 18 months (P = .03) and 24 months (P = .004).

Data source: A randomized study of 498 patients with extensive-stage small-cell lung cancer responding to initial chemotherapy.

Disclosures: Dr. Slotman and his coauthors reported no financial disclosures.

PATRICE WENDLING/FRONTLINE MEDICAL NEWS

Dr. Ben J. Slotman: Adding thoracic radiation may improve overall survival.

RADIANT: Mixed results for adjuvant erlotinib in NSCLC

BY PATRICE WENDLING
Frontline Medical News

CHICAGO – The phase III RADIANT trial of adjuvant erlotinib failed to meet its primary endpoint in early-stage, resected non–small cell lung cancer, but shores up support for adjuvant EGFR tyrosine kinase inhibitors in patients with an EGFR mutation.

RADIANT sought to determine whether adjuvant erlotinib (Tarceva) 150 mg/day, with or without chemotherapy, would prolong disease-free survival (DFS) in patients with completely resected stage IB to IIIA epidermal growth factor receptor (EGFR)–positive non–small cell lung cancer (NSCLC).

Erlotinib, an EGFR tyrosine kinase inhibitor (TKI), has proven efficacy in advanced-stage NSCLC in several settings: as second- and third-line therapy in unselected patients, first-line maintenance therapy in unselected patients, and first-line therapy in patients with EGFR-activating mutations.

Among all 973 randomized patients, however, the study's primary endpoint of median disease-free survival (DFS) was not significantly different at 48.2 months for placebo and 50.5 months for erlotinib (hazard ratio, 0.90; P = .32), Dr. Karen Kelly reported at the annual meeting of the American Society of Clinical Oncology.

The median duration of treatment was noticeably shorter with erlotinib (11.9 months vs. 21.9 months).

At a median follow-up of 47 months, overall survival (OS) data were immature, she said. At the time of the analysis, there were 95 events in the placebo arm and 182 events in the erlotinib arm (HR, 1.13; P = .33), with the median not yet reached.

It was hoped the results of RADIANT would also clarify the broader question of whether adjuvant treatment with EGFR TKIs improves outcomes for patients whose tumors harbor an EGFR mutation.

In a subset analysis of 161 patients with deletion 19 or L858R EGFR mutations, median DFS favored erlotinib at 46.4 months vs. 28.5 months for placebo (HR, 0.61; P = .0391).

This 18-month difference, however, was not statistically significant because the study's hierarchical testing procedure dictated that if the primary endpoint was not met all subsequent endpoints would be deemed nonsignificant, explained Dr. Kelly of the University of California–Davis Comprehensive Cancer Center, Sacramento.

Exposure to erlotinib and placebo was similar in the EGFR-mutated subgroup (median 21.2 months vs. 21.9 months). Importantly, patients treated with placebo had more stage IIIA disease at baseline (30.5% vs. 17.6%), she noted.

Median OS in the mutation-positive subset was

Invited discussant Dr. Nasser Hanna of the Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, called the data of adjuvant erlotinib in patients with an activating EGFR mutation "persuasive and compelling."

Enthusiasm for adjuvant EGFR TKI therapy for early-stage NSCLC has wavered in light of the consistent development of acquired resistance to EGFR TKIs in metastatic disease, and data from two randomized trials showing that the EGFR TKI gefitinib (Iressa) did not improve survival in advanced NSCLC and was potentially detrimental after chemoradiotherapy plus docetaxel in stage III disease.

The results prompted the premature closure of the Canadian phase III BR19 trial of adjuvant gefitinib in completely resected stage 1B-IIIA NSCLC, which reported no DFS or OS benefits from gefitinib in the total population or in the 15 patients with EGFR mutations (J. Clin. Oncol. 2013;31:3320-6).

To put the current subset analysis in perspective, however, Dr. Hanna pointed out that the magnitude of gain in DFS with adjuvant EGFR TKI therapy is now consistent across three datasets: RADIANT, the phase II SELECT trial, and an analysis by Memorial Sloan-Kettering Cancer Center (MSKCC), New York (J. Thorac. Oncol. 2011;6:569-75).

Two-year DFS with adjuvant erlotinib was 89% in patients with completely resected stage I-III NSCLC with EGFR exon 19 or 21 mutations treated at MSKCC, after controlling for stage, type of surgery, and adjuvant platinum chemotherapy.

RADIANT *continued on page 17*

VITALS

Key clinical point: Adjuvant EGFR TKI therapy may delay disease progression in NSCLC patients harboring an EGFR mutation.

Major finding: Median DFS in patients with EGFR-mutant NSCLC was 46.4 months with adjuvant erlotinib and 28.5 months with placebo (HR, 0.61; P = .0391).

Data source: A prospective study in 973 patients with stage IA-IIIA NSCLC.

Disclosures: Dr. Kelly and Dr. Hanna reported no relevant disclosures. Several coauthors reported financial relationships with Astellas Pharma, Roche, OSI Pharmaceuticals, or Novella Clinical.

CREST *continued from previous page*

most 90% still had persistent intrathoracic disease at the time of randomization. Their median age was 63 years.

Overall survival at 1 year was not statistically different between the TRT and no TRT arms (33% vs. 28%; hazard ratio, 0.84; $P = .066$). The survival curves began to diverge after 9 months, however, leading to a significant overall survival benefit favoring TRT at 18 months ($P = .03$) and 24 months (13% vs. 3%; $P = .004$), Dr. Slotman said.

A subgroup analysis found no influence on overall survival for treatment factors such as age, sex, response after chemotherapy, or presence of intrathoracic disease at randomization.

It will be important to know whether patients with extensive-stage disease receiving thoracic radiotherapy also have less progression of thoracic disease.

Discussant Dr. Walter J. Curran Jr., executive director of the Winship Cancer Institute of Emory University, Atlanta, said CREST was a well-executed and adequately powered trial, but argued that its conclusion that thoracic RT improves overall survival "is not supported by the presented data."

The hazard ratio of 0.84 failed to reach the HR goal of 0.76, and the comparison at 2 years was not the primary end point of the trial, he said.

Dr. Curran said there is a rationale for why sequential chemotherapy-radiation would work for patients with more extensive disease, even though every randomized limited disease small-cell trial has shown a benefit with concurrent vs. sequential chemotherapy-radiation therapy or early vs. delayed concurrent chemoradiation, and little to no benefit with sequential chemoradiation, compared with chemotherapy alone.

"The rationale behind it, and it's a reasonable one, is that in the noncurative setting, which is what we're dealing with if you remember the survival curves Dr. Slotman showed us, we really are probably talking about debulking chemoresistant disease," he said. "If one is able to do that with limited toxicity and without long-lasting morbidity, that might extend survival but certainly is not going to procure cure rates as thoracic radiation can do in limited disease."

Progression-free survival was significantly better in patients receiving TRT vs. no TRT (HR, 0.73; $P = .001$), Dr. Slotman said.

TRT-treated patients also had significantly less intrathoracic progression overall (43.7% vs. 80%; P less than .001), as the first site of relapse (41.7% vs. 78%; P less than .001), and as the only site of relapse (20% vs. 46%; P less than .001).

Going forward, Dr. Curran said it will be important to know whether patients with extensive-stage disease receiving TRT also have less progression of thoracic disease and to better understand quality of life and toxicity associated with the therapy.

Dr. Slotman said grade 3/4 toxicity was similar between groups, although those receiving radiation had a modest increased risk of grade 3 fatigue (11 vs. 8 events) and grade 3 esophagitis (4 events vs. 0 events).

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RADIANT *Continued from page 15*

Data reported from SELECT at this year's ASCO (Ab. 7514) showed 2-year DFS was also 89% with adjuvant erlotinib in EGFR mutation–positive NSCLC, and reached 96% in stage I and 91% in stage III disease, he said.

"We don't have just one data point; we have three data points that are consistent," Dr. Hanna said. "This magnitude of gain is substantial and it is significant, and it appears potentially far more than with adjuvant chemotherapy."

He said the jury is still out on overall survival, but observed that the Food and Drug Administration granted accelerated approval for imatinib (Gleevec) in KIT-mutant gastrointestinal stromal tumors based on DFS alone.

In an interview, Dr. Hanna said he has never used an EGFR TKI in any disease setting except the metastatic setting, and though persuasive, the RADIANT, SELECT, and MSKCC data are not conclusive and that a phase III trial is planned.

The jury is still out on overall survival, but the FDA granted accelerated approval for imatinib (Gleevec) in KIT-mutant gastrointestinal stromal tumors based on DFS alone.

"I know that other experts have been using erlotinib in the adjuvant setting, though, off of a clinical trial," he said. "I've struggled with the issue, but I don't think I'm ready to go there yet."

Dr. Kelly said the safety profile of erlotinib was generally consistent with that observed in the advanced disease setting and that additional biomarker analyses are ongoing.

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VIEW ON THE NEWS

Dr. Lary Robinson, FCCP, comments: Adjuvant chemotherapy is generally recommended in resected Stage IB (>4 cm diameter), stage II and III NSCLC. The randomized phase III RADIANT trial sought to demonstrate whether adding the tyrosine kinase inhibitor erlotinib to adjuvant therapy for resected EGFR-positive patients would further improve disease-free survival.

Unfortunately, there was no difference in the entire 973 patients randomized to erlotinib versus placebo. But a subset analysis of patients with the more sensitizing EGFR mutations (deletion 19 or L858R) who represented 16% of the overall patients showed an impressive DFS advantage in the erlotinib group compared with placebo (46.4 mo. vs. 28.5 mo.).

Although the data are compelling, further planned trials will likely verify whether erlotinib is recommended routinely as adjuvant therapy in selected EGFR-positive resected NSCLC patients.

COMMENTARY: What prevails in hospital-vs.-medical staff disputes

BY S.Y. TAN, M.D., J.D.

QUESTION: The medical staff at the newly opened hospital is putting together a set of bylaws covering credentialing, peer review, and patient-care quality assurance. The doctors are mostly independent contractors and not hospital employees. The administration, obsessed with financial solvency, wishes to retain veto power over decisions affecting staff privileges. In potential disputes affecting the hospital and its medical staff, which of the following is true?

A. The Joint Commission subscribes to the view that hospital administration rather than medical staff has overall authority over clinical privileges decisions.
B. Economic credentialing is universally regarded as unethical and illegal.
C. Medical bylaws are a contractual agreement.
D. A hospital can never make unilateral changes in the medical staff bylaws.
E. The medical staff is an integral part of the hospital's organizational structure, with its powers wholly independent of the hospital's governing board.

BEST ANSWER: A. Doctors with hospital privileges typically organize themselves into a formal medical staff, with its powers derived from the hospital's governing board. Professional organizations such as the American Medical Association believe that the medical staff of a facility should be self-governing, with its own enforceable set of bylaws. The general view is that these bylaws do not create a binding contractual agreement.

For example, when Dr. George T. O'Byrne sued Santa Monica–UCLA Medical Center where he held medical staff privileges, the California Court of Appeal ruled that the hospital's fiduciary duty is to its shareholders and the public – but not to its physicians – and that the medical staff bylaws did not constitute a contract (*O'Byrne v. Santa Monica-UCLA Medical Center*, 114 Cal.Rptr.2d 575 [Cal. Ct. App. 2001]).

A similar situation appears to hold in Minnesota, where the medical staff accused Avera Marshall Regional Medical Center of unilateral credentialing and revision of the bylaws, and interference with quality assurance operations (*Avera Marshall Medical Staff v. Avera Marshall Regional Medical Center*, 836 N.W.2d 549 [Minn. Ct. App. 2013]). Both the trial court and the court of appeals have held that the medical staff lacked the legal capacity to bring a lawsuit and that the bylaws were not a contract (the final decision of the Minnesota Supreme Court is pending).


DR. TAN

The Joint Commission's view is that the hospital administration has the ultimate authority over clinical privileges of its medical staff, in support of the legal doctrine that a hospital can be held liable for the torts of its practitioners. This notion of corporate liability, which includes negligent credentialing, stemmed from the seminal *Darling* case (*Darling v. Charleston Community Hospital*, 211 N.E.2d 253 [Ill. 1965]) where the court held the hospital liable for failing to adequately review the qualifications and performance of a negligent medical staff member. Dr. Alexander, the doctor at issue, had applied a plaster cast too tightly, which caused the college football player to eventually lose his leg.

Other cases followed, including the infamous California case of *Gonzales v. Nork*, 573 P.2d 458 (Cal. 1978), in which a drug-abusing doctor misrepresented himself as being qualified to perform laminectomies. Even in jurisdictions that do not specifically recognize negligent credentialing as a legal cause of action, supreme courts have allowed this legal theory to go forward.

Two recurring issues tending to embroil hospital and staff in conflict are unilateral actions by a medical center and the use of economic credentialing.

The usual procedure for amending the bylaws is for the medical staff to initiate and approve changes before subjecting them for final endorsement by the hospital board. Thus, when a Florida hospital unilaterally refused to re-credential two qualified radiation oncologists because of its intention to exclusively contract with the University of Miami School of Medicine for all radiation oncology procedures, the jury found in favor of the aggrieved doctors, awarding them $2.5 million in lost profits and $20.25 million in punitive damages (*Columbia/JFK Medical Center v. Spunberg*, 784 So.2d 541 (Fla. App. Ct. 2001).

Likewise, a small Georgia hospital tried to close its cardiology department in order to enter into an exclusive contract with a separate group of cardiologists. The Georgia Court of Appeals held that a hospital could not deprive physicians of access to its facilities unless stated in the bylaws or specifically agreed to in an individual contract (*Satilla Health Services v. Bell*, 633 S.E.2d 575 [Ga. Ct. App. 2006]).

However, under some narrow circumstances, a hospital can act unilaterally, without medical staff agreement, especially where the bylaws are silent on the point. Illinois recently ruled that a medical center could, without physician assent, increase physician malpractice premium limits to $1,000,000 per occurrence and $3,000,000 aggregate for multiple occurrences (from $200,000 and $600,000, respectively). Its appellate court allowed the change, holding that physician enforcement of its bylaws were restricted only to matters of clinical competence (*Fabrizio v. Provena United Samaritans*, 857 N.E.2d 670 [Ill. S.Ct. 2006]).

A second area of conflict between doctors and hospitals is hospitals' use of economic factors in credentialing, where financial factors are used to profile – and determine – a physician's application for privileges.


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For example, a staff gynecologist risked losing her 19-year membership at Baptist Health Medical Center in Little Rock, Ark., because her physician-husband owned an interest in a competing hospital specializing in spinal surgery. The case settled when the husband divested his competing ownership. In Arkansas, the courts have ruled that Baptist Health's policy wherein a physician who holds a financial interest in a competing hospital is ineligible for privileges at any Baptist Health hospital is both unconscionable and illegal, and the hospital economic credentialing policy tortiously interfered with the physicians' existing and prospective business relationships (*Murphy v. Baptist Health*, 373 S.W.3d 269 [Ark. 2010]).

But other jurisdictions have not adopted this view. The South Dakota Supreme Court has ruled that a hospital administration may refuse applicants to the medical staff based on economic criteria (*Mahan v. Avera St. Luke's*, 621 N.W.2d 150 [S.D. S.Ct. 2001]). The court questioned the legal right of certain members of the medical staff to open a competing ambulatory surgery center. In a subsequent case, the same court held that in the absence of specific prohibitions in the bylaws, a hospital could use economic credentialing in its staffing determinations.

Even for physicians with only an occasional hospital practice, the following pointers from the book "The Biggest Legal Mistakes Physicians Make and How to Avoid Them," edited by Steven Babitsky and James J. Mangraviti Jr., may prove useful: 1) Failing to practice in a collegial manner.

Law & Medicine *continued on following page*

VIEW ON THE NEWS

Dr. Vera DePalo, FCCP, comments: The practice of medicine and the delivery of health care are complicated. The legal issues surrounding all aspects of that practice and delivery result in additional layers of complexity. The laws of the land in 50 states, the decisions handed down in legal cases, and the opinions of regulatory bodies add even more intricacy.

At the end of the day, we owe it to our patients to pass everything through the filter of staying "patient-centered" and considering the impact on them. Whether the issues are on the medical staff side or the hospital administration side, we are all in the business of health care and our patients should come first.

COMMENTARY: Should you hire a social media consultant?

BY JEFFREY BENABIO, M.D.

Over the last few years, I have spoken with hundreds of physicians who tell me that they want to be engaged on social media, but they just don't have the time or resources. I understand. If this sounds like you, then it's time to consider hiring a social media consultant.


DR. BENABIO

Hiring the right social media consultant or agency can provide many benefits, including:

► Shaping and marketing your brand.
► Handling daily social media updates and tasks.
► Devising a strategic plan to engage with social media influencers in your specialty.
► Developing a strategic plan to engage with your desired audience. Do you want new patients? More traffic to your practice website?
► Directing you to the best social media platforms for your specific goals, such as Facebook, YouTube, or Pinterest.
► If applicable, developing a plan to promote and market your products and unique services.
► Coaching you and your staff to become better and more efficient at social media.
► Helping you navigate social media analytics.
► Taking the stress off doing it yourself.

There is no foolproof formula for

Continued on following page

Law & Medicine *continued from previous page*

2) Impugning the quality of care of the hospital, nurses, and other physicians.
3) Not knowing the hospital's policies and procedures.
4) Not involving consultants when the issue is out of one's specialty.
5) Not accepting constructive criticism and suggestions.
6) Failing to seek approval before prescribing unorthodox drugs or treatment.
7) Failing to respond promptly to inquiries about care or behavior.
8) Failing to follow up on an agreement resolving an issue.
9) Acting as though the hospital is lucky to have such a physician.
10) Not calling a lawyer when necessary.

Dr. Tan is professor emeritus of medicine and former adjunct professor of law at the University of Hawaii. This article, which originally appeared in the "Law & Medicine" column series in INTERNAL MEDICINE NEWS, *is meant to be educational and does not constitute medical, ethical, or legal advice. Some of Dr. Tan's articles are adapted from his 2006 book, "Medical Malpractice: Understanding the Law, Managing the Risk," and his 2012 Halsbury treatise, "Medical Negligence and Professional Misconduct." For additional information, readers may contact the author at siang@hawaii.edu.*

Continued from previous page

choosing the best social media consultant for your practice, but here are some key points to keep in mind when considering candidates:

► Do they have experience? How long have they been consulting? How many clients have they had? How many do they currently have? Have they been published online or in print magazines? Do they teach any courses, either online or in person? Do they have success stories they can share?

► Check out their website. Is it modern? User friendly? Does it include bios of the employees and client testimonials?

► Check out their social media involvement. Are they actively engaged on social media sites that they suggest you use? Look at their Facebook, Twitter, LinkedIn, and Pinterest accounts, as well as any other sites they may use.

► Are they willing to create unique content for your practice? Some agencies create boilerplate content that they use on multiple client sites. You want to be certain that the content they create for your practice aligns with your marketing and branding goals.

► Do you like them? This is a critical question because social media is, by nature, social. Do the staff members of your potential agency have likable personalities? Are they good listeners? Do they respond promptly to e-mails and phone calls? Do they seem confident or perpetually stressed?

► Do they understand your business? If the firm you hire has only restaurants as clients, then you might be at a disadvantage. Make certain that the firm that you choose understands your area of medicine and has a track record of success with medical practices.

Interview several firms before choosing one. The price ranges dramatically. Some agencies might charge $300 a month, while others might charge $3,000.

► Do they have clearly defined costs? Many companies will offer pricing based on 1- to 3-month intervals. Will they be creating and posting new content daily, weekly, biweekly? Will they work weekends and off-hours? How frequently will they meet with you in person? All of these factors will affect price. Of course, the more hands-on your social media consultants are, the higher the price is likely to be.

Outsourcing your social media is a decision that you and staff must consider carefully. As with most important decisions, it's advisable to interview several different firms before choosing one. As for price, it ranges dramatically. Some agencies might charge $300 a month, while others might charge $3,000. It's up to you and your office staff to determine which agency is best suited for your practice's budget, needs, and goals.

In my next column, I'll address pitfalls to avoid when choosing a social media consultant or agency.

Dr. Benabio is a partner physician in the department of dermatology of the Southern California Permanente Group in San Diego and a volunteer clinical assistant professor at the University of California, San Diego. Dr. Benabio is @Dermdoc on Twitter.

NETWORKS: Smoking's toll, posttransplant infections, EHRs

Women's Health

A decade lost: The real life cost of tobacco use

Smoking prevalence among women peaked in the 1960s, about 20 years later in women than in men, so previous studies might have considerably underestimated the full risks of smoking. The extent of the 21st century hazards of a lifetime of smoking and the benefits of quitting have recently been clarified in two large cohort studies in the United Kingdom and United States.

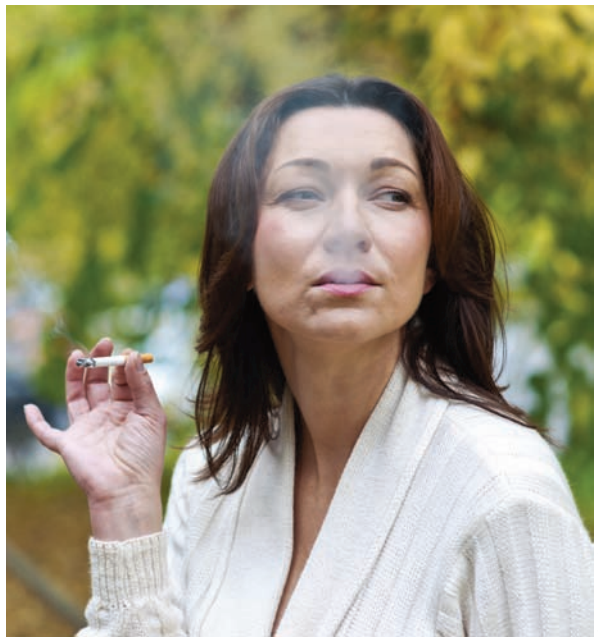
In the Million Women Study, Dr. Pirie and colleagues reported on the hazards of smoking in a prospective cohort study of 1.2 million women recruited between 1996-2001 in the United Kingdom (*Lancet*. 2013;381[9861]:133). At baseline, patients were sent questionnaires about lifestyle, medical history, smoking history, and socio-demographics. Nearly all women were followed to 2011 through mortality records.

In the US National Health Interview Survey (NHIS), Dr. Jha and colleagues reported results of a large, prospective, nationally representative study of smoking and its relation to mortality in 113,752 women and 88,496 men 25 years of age or older to provide estimates of the 21st century hazards of smoking and the benefits of smoking cessation (*N Engl J Med*. 2013;368[4]:341).

Results were similar in both studies. In the Million Women Study, female smokers lost, on average, 11 years of life, compared with nonsmokers. The age at which women had first started smoking regularly affected overall mortality decades later. Those who had started at about age 15 were at greater risk than those who had started only 4 years later. In the NHIS study, men lost an average of 12 years. Women who smoked throughout their adult life were three times as likely to die prematurely from smoking-related diseases compared with nonsmokers. The most common causes of death were from smoking-related neoplastic, vascular, or respiratory diseases.

The silver lining in the Million Women Study was that women who stopped smoking by age 40 demonstrated a mortality rate only 1.2 times that of never-smokers, avoiding 90% of the excess hazard for continued smokers. Women who stopped by age 30 avoided an impressive 97% of the excess hazard. Similar absolute benefits of cessation were seen in the NHIS study.

In both studies, benefits of cessation were considerable—the earlier, the better. As Dr. Jha's report noted, "Smoking is associated with a decade of lost life, and cessation reduces that loss by about 90%." This powerful message needs to reach the public. The American College of Chest Physicians (CHEST) provides educational resources for smoking prevention and cessation. For the last 15 years, CHEST has organized lung health education in elementary schools in cities where annual CHEST meetings are held. We need to reach a larger population. Working with young adults in our communities would help. In this era of technology, innovative techniques, such as interactive, individualized text messaging aimed at specific groups (eg, adolescents, young adults, and pregnant women), may have an impact. This approach combined with public health policies, pharmacotherapy, and counseling will help our patients stay healthier and live longer.



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The Million Women Study indicated that those who quit smoking by age 40 avoided most excess hazards.

Dr. Janet Myers, FCCP, Ex Officio
and Dr. Pratibha Kaul, FCCP, NetWork Chair

Continued on following page

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From October 25 - 30, we will be situated in a city as unique as our annual meeting. Austin, Texas, will be the home for CHEST 2014, and it couldn't be more fitting. While Austin surprises you with its distinctive charm, CHEST 2014 will delight you with cutting-edge education presented in many different learning formats.

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What makes Austin unique?

Austin locals are proud of the Keep Austin Weird Festival and 5K. This annual event is full of music, costume contests, food, and crafts and reflects the creative culture of Austin. In the traditional state of Texas, Austin stands out for being on the forefront of the live music scene, offering an eclectic mix of culinary offerings and featuring unique landmarks admired by both tourists and locals.

Browse chestmeeting.chestnet.org for our recommendations on local cuisine and live music. If you're truly looking to embrace the "weirdness," here are some interesting landmarks that you won't find anywhere else.

Congress Avenue Bridge – Austin is home to the largest, urban bat colony in North America. 1.5 million Mexican, free-tail bats reside at the Congress Avenue Bridge. The bats take flight at dusk every night, and you can watch the incredible sight from atop the bridge, below in the park, or on a riverboat cruise.

SunFlowers – 15 giant sunflowers were created using photovoltaic solar panels along a bike path on I-35. These panels absorb the sun's energy, beam blue patterns on the ground, and provide shade along the bike path below. At night, the path is lit up in blue from the SunFlowers' solar-powered LED lights.

Museum of the Weird – This museum features oddities like mummies, shrunken heads, giant lizards, a Bigfoot display, and a ghost exhibit.

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Continued from previous page

Transplant

Community-acquired respiratory viral infections following lung transplantation

Pharmacologically induced immunosuppression is a necessity in order to ensure allograft tolerance following lung transplantation (LTX). Unfortunately, suppression of the immune system potentially predisposes the recipient to complications arising from infections due to community-acquired respiratory viruses (CARVs), the consequences of which are being increasingly recognized.

Five CARVs increasingly emerge as respiratory tract pathogens after LTX: respiratory syncytial virus (RSV), parainfluenza virus (PIV), influenza virus, human metapneumovirus (MPV), and adenovirus. Acute infections with these agents may impart an abrupt decline in allograft function (~25% of the FEV_1), with most recipients regaining their lost function within weeks. Still others are plagued by permanent decrements with subsequent mortality ranging between 3% and 20%. Of those who recover, a higher relative risk of development of chronic allograft dysfunction in the form of bronchiolitis obliterans syndrome (BOS) within 1 to 2 years[1] has been reported. During the 2009 outbreak of the H1N1 flu virus, up to 75% of infected LTX recipients experienced a transient decrease in allograft function after which 33% of those afflicted developed BOS within 1 year.

As effective treatments for CARVs are limited, the best therapy remains prevention. For prophylaxis against influenza infection, only the inactivated injectable vaccine should be administered each year to LTX recipients and their family contacts. Should influenza infection occur, an extended treatment course of a neuramidase inhibitor, such as oseltamivir is recommended. With respect to RSV and PIV infections, it has been suggested that treatment with aerosolized ribavirin may be effective and furthermore may decrease the incidence of subsequent development of BOS.[2] Unfortunately, treatments for other CARV infections are less well-defined with some experts recommending trials of corticosteroids and infusions of immunoglobulins in such cases.

In summary, when infections due to CARVs occur among LTX recipients, they impart significant risk for both acute- and long-term allograft dysfunction, the best treatment for which remains an effective prevention strategy.

Dr. David R. Nunley
NetWork Vice-Chair

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Practice Operations

The burden of quality reporting measures using EHRs

There has been a widespread adoption of electronic health records (EHRs) across the country, following the American Recovery and Reinvestment Act of 2009 incentive program. A key principle of the meaningful use of the incentive program is to report on quality measures. This massive EHR adoption was followed by the widespread need to report quality by reusing data from EHRs.

The rapidly increasing volume of hospital quality measures and the linkage of quality measures to payment underscore the need for high-quality measures reporting solutions that are generated from EHR data. These EHR data are feasible to collect in an automated fashion, generate valid and reliable results, and demonstrate benefit that outweighs the cost, if implemented correctly.

One would assume that these quality measures data are automatically available and ready to be reported since "all the data are there." Not so simple.

DR. BASSILY-MARCUS

What is grossly underestimated is the infrastructure that is needed to identify, collect, assess, and validate the data to produce reliable reports that accurately reflect the clinical activity that is taking place. A degree of chart abstraction that is supported by varying levels of automation is required. This process is typically more challenging than anticipated, requiring multiple iterations of workflow redesign, data capture, quality measure calculation, and validation.

The burden of developing, testing, and validating these quality reports is placed on hospitals, physician practices, and IT staff with the underappreciated need of tremendous financial and human resources.

Regulatory agencies should consider the added direct and indirect cost for quality measures reports when considering these additional quality metrics requirements.

Developing and implementing quality measures, while helpful, may incentivize hospitals and their staff to focus on improving performance scores without necessarily reflecting actual improvement in patient care and outcomes. The impact on patient outcomes is yet to be seen.

Dr. Adelle Bassily-Marcus
NetWork Steering Committee Member

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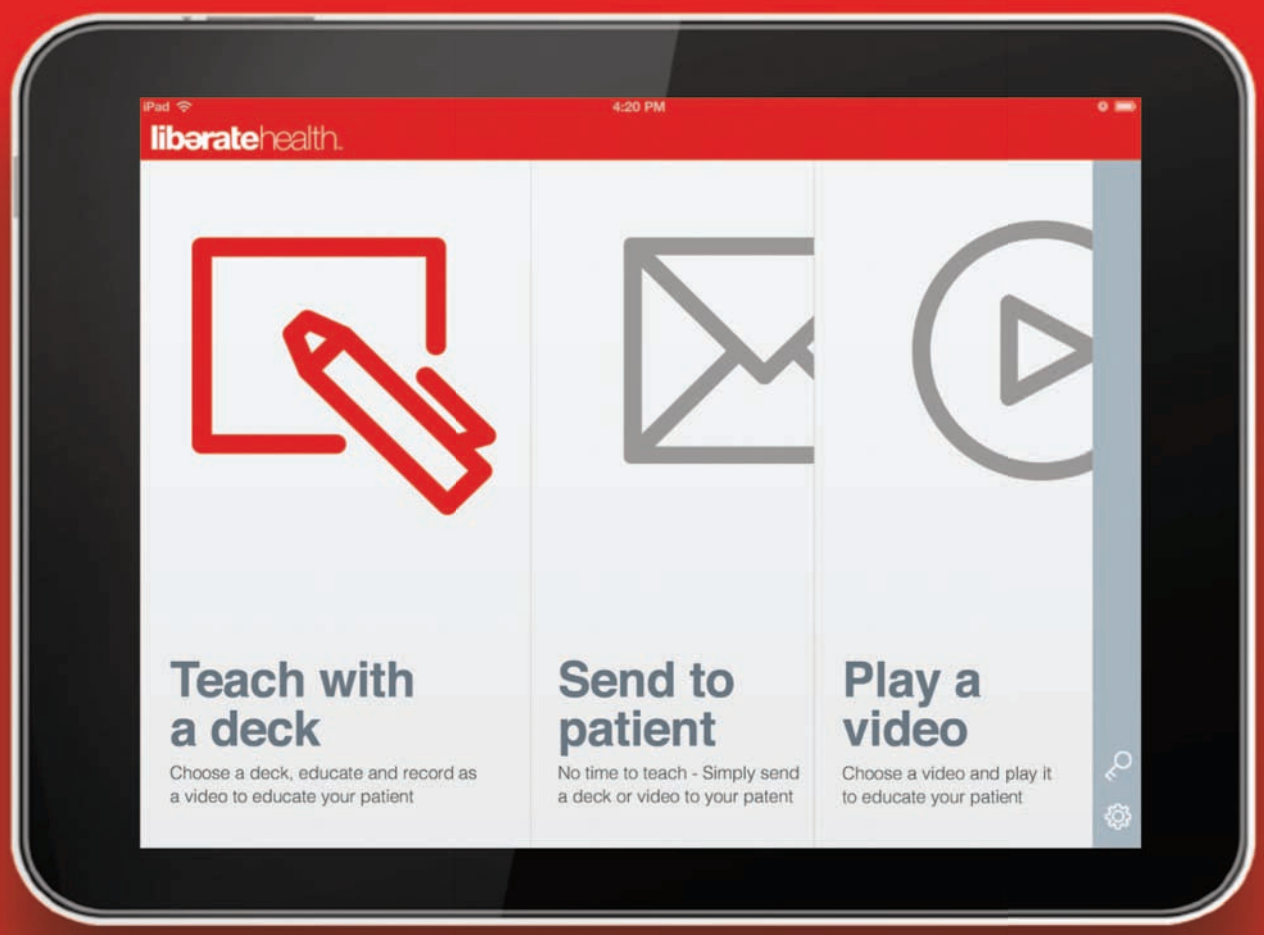

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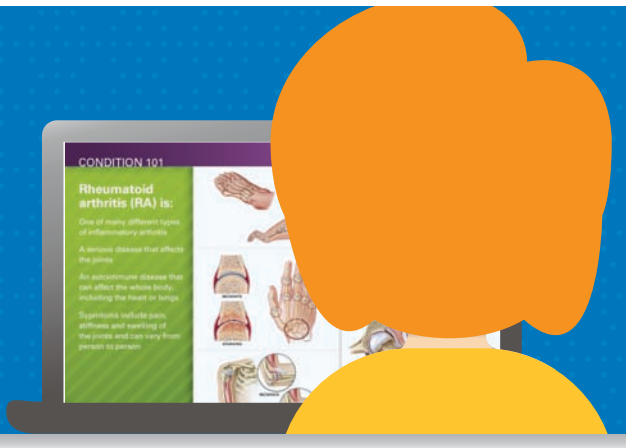

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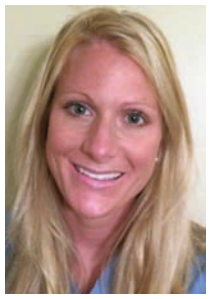
Selenium and zinc eyed as sepsis therapies

Micronutrients *from page 1*

cellular antioxidant system as a structural component of the selenoprotein enzymes, including glutathione peroxidase. These enzymes catalyze the reduction of hydroperoxidases to less toxic products, thereby protecting cells against oxidative stress. Selenium can also modulate the inflammatory cascade by inhibiting pro-inflammatory gene expression.



DR. SANDQUIST

DR. WONG

Selenium plasma concentrations are significantly lower in critically ill patients compared with age-matched healthy control subjects. Current evidence suggests that selenium concentrations are lowest in patients with sepsis and that low plasma selenium concentrations correlate with poor outcomes and organ

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failure (Alhazzani et al. *Crit Care Med*. 2013;41[6]:1555). Whether these associations represent pathological responses or epiphenomena is not entirely known. Nonetheless, because selenium is critical for the selenoprotein enzymes that function in antioxidant defense, it is biologically plausible that selenium supplementation may improve the outcomes of patients with sepsis.

A recent clinical trial (Heyland et al. *N Engl J Med*. 2013;368[16]:1489) showed that early administration of glutamine and/or a combination of antioxidants (selenium, zinc, beta-carotene, vitamin C, and vitamin E) did not improve mortality in critically ill adults with multiorgan failure. Glutamine administration was actually associated with increased mortality in this study.

This trial offers strong evidence that selenium administration, in combination with other antioxidants, does not improve clinical outcomes in critically ill patients, although it is difficult to assign effect to any one micronutrient, as selenium was administered in combination with other agents. Furthermore, this study enrolled patients with heterogeneous forms of critical illness, thereby making it difficult to isolate any beneficial effect in more specific conditions, such as sepsis.

A recent meta-analysis by Alhazzani and colleagues (*Crit Care Med*. 2013;41[6]:1555) examined the effect of isolated selenium supplementation on mortality in critically ill patients with sepsis. They reported a trend toward reduced mortality (odds ratio for mortality = 0.73, P =.03) in patients receiving selenium at higher than the daily recommended dose. Selenium supplementation had no effect on secondary outcomes, including a reduction of nosocomial pneumonia or length of stay. The quality of this evidence was graded as "low" based on the high risk of bias and imprecision, but the authors encouraged further well-designed trials addressing the efficacy of selenium supplementation in sepsis.

A trial of IV selenium supplementation in sepsis was recently completed by the German Sepsis Network with an estimated total enrollment of 1,180 subjects (clinicaltrials.gov: NCT00832039). The primary outcome of this study was all-cause mortality at 28 days. This study, when published, may provide more conclusive evidence to support or oppose selenium supplementation in sepsis.

Zinc

Zinc supplementation may also have a therapeutic role in sepsis. Zinc is involved in both innate and adaptive immune function. Notably, zinc-deficient states produce lymphopenia, impaired natural killer and phagocytic cell function, and impaired cytokine production. Zinc directly regulates signal transduction mechanisms involved in immunity and inflammation. Zinc also serves important roles in oxidative stress responses, neurocognitive function, growth, and development.

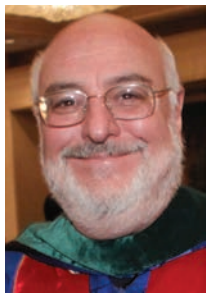
Metallothioneins are metal-binding proteins involved in zinc homeostasis. They serve roles in the scavenging of free radicals, detoxification of heavy metals, and participate in the inflammatory response to stress. It has been estimated that approximately 10% of the human proteome potentially interacts with zinc (Andreini et al. *J Proteome Res*. 2006;5[1]:196).

Transcriptomic studies demonstrated that within 1 day of admission for septic shock, children's genomes demonstrate decreased expression of a large number of genes involved in zinc homeostasis (Wong et al. *Physiol Genomics*. 2007;30[2]:146). When comparing pediatric survivors with nonsurvivors of septic shock, nonsurvivors had significantly lower serum zinc concentrations. Furthermore, metallothionein expression was increased in the nonsurvivors, suggesting a functional consequence of altered zinc homeostasis.

The role of metallothionein expression and zinc homeostasis was further investigated in a study involving a heterogeneous cohort of critically ill children (Cvijanovich et al. *Pediatr Crit Care Med*. 2009:10[1]:29). All patients in this study had low serum zinc concentrations on days 1

Continued on following page

EDITOR'S COMMENT



Drs. Sandquist and Wong present a significant and up-to-date review of potentially promising and, what would seem, common sense therapies for sepsis. Despite this, the literature has not yet shown significant benefit to antioxidants and elemental replacement; in fact, glutamine has shown questionable harm. There is a number of large trials underway and, hopefully, these results might help clear the haze. Selenium and zinc supplementation may prove to be significant primary and adjunctive therapies but to which patients remains truly unclear. Sepsis being such a heterogeneous entity, that it is still not surprising that the "one size fits all approach" does not give us clear answers, but we continue to try to find these potential solutions.

Dr. Peter Spiro, FCCP
Section Editor

Continued from previous page

and 3 of illness. Furthermore, on day 1 of illness, there was a positive correlation between zinc levels and metallothionein protein expression.

Several murine models have demonstrated the efficacy of zinc supplementation in sepsis. Zinc deficiency increased the bacterial burden and enhanced lung NF-kappa-B activity in a mouse model of sepsis, and short-term zinc supplementation reversed these effects (Bao et al. *Am J Physiol Lung Cell Mol Physiol*. 2010;298[6]:L744). Mouse mortality from polymicrobial sepsis was significantly increased with zinc deficiency and correlates with higher plasma cytokines, increased oxidative tissue damage, and cell death in the lungs and spleen of zinc-deficient animals (Knoell et al. *Crit Care Med*. 2009;37[4]:1380). These biological effects were diminished, and mortality improved in deficient mice that received zinc supplementation following septic injury. Another study demonstrated decreased mortality and bacterial load in septic mice receiving zinc supplementation for 3 days prior to septic injury compared with unsupplemented control mice (Nowak et al. *Pediatr Crit Care Med*. 2012;13[5]:e323).

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In contrast to the murine studies, the trial by Heyland and colleagues did not demonstrate improved mortality in critically ill adults with multiorgan failure who received zinc supplementation in combination with other micronutrients. In another recent clinical trial, critically ill children were randomized to receive either whey protein supplementation or a cocktail of zinc, selenium, glutamine, and metoclopramide (Carcillo et al. *Pediatr Crit Care Med*. 2012;13[2]:165). There was no difference in the primary endpoint—time to nosocomial infection—between the two groups. However, in a secondary analysis, there was a reduced nosocomial infection rate in the immunocompromised subgroup members who received the antioxidant cocktail, suggesting that zinc supplementation may be useful in patients who are particularly infection-vulnerable.

Although zinc supplementation in combination with other antioxidants has been trialed in critically ill patients, the effect of zinc alone has not been fully explored. Investigators at Children's Hospital and Research Center Oakland (clinicaltrials.gov: NCT01062009) recently completed a phase 1 safety and dose-finding trial of IV zinc supplementation in critically ill pediatric patients. Investigators at the University of Vermont (clinicaltrials.gov: NCT01162109) are exploring the safety and pharmacokinetics of IV zinc supplementation in critically ill adults with severe sepsis. The results of these trials will help to inform the future design of studies to test the efficacy of zinc supplementation in pediatric and adult sepsis.

Summary

Although selenium and zinc levels are decreased in pediatric and adult patients with sepsis, it is not clear whether correcting these alterations is of clinical benefit. Recent human trials investigating selenium supplementation are difficult to interpret in the context of sepsis as many have been conducted in patient populations that include heterogeneous forms of critical illnesses and have often included selenium in combination with other micronutrients.

The recent meta-analysis by Alhazzani and colleagues, however, provides evidence that isolated selenium supplementation may be effective in reducing mortality in patients with sepsis. The results of the recently completed clinical trial by the German Sepsis Network may provide conclusive evidence to confirm this trend. While animal studies supporting zinc supplementation in sepsis abound, human trials have investigated zinc in combination with other antioxidants, and phase 1 trials of zinc alone are only currently underway. Further large, randomized trials will be needed before zinc supplementation can be considered efficacious in reducing mortality in sepsis.

Dr. Sandquist is a pediatric critical care medicine fellow, Department of Pediatrics, University of Cincinnati College of Medicine; Dr. Wong is a Professor of Pediatrics and the Director of the Division of Critical Care Medicine, Cincinnati Children's Hospital Medical Center and Cincinnati Children's Hospital Research Foundation, Cincinnati, Ohio.

CHEST Global Headquarters receives LEED Silver Certification

We are proud to announce the CHEST Global Headquarters has been granted LEED Silver Certification. LEED, or Leadership in Energy and Environmental Design, is a certification program recognized around the world as the premier mark of achievement in green building. LEED certification is pursued by businesses and organizations serious about conserving energy, reducing water consumption, improving indoor air quality, making better building material choices, and driving innovation.

Committed to being socially and environmentally responsible, CHEST made a deliberate decision to build to LEED specifications. The features and practices implemented to achieve Silver Certification reach far beyond the boundaries of the building site to reduce CHEST's carbon footprint now and in the future—a significant and conscientious achievement.


ACCP

Committed to environmental responsibility, CHEST is celebrating the LEED Silver Certification of its new headquarters in Glenview, Illinois.

This Month in *CHEST:* Editor's picks

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

Outcomes for Patients With Cancer Admitted to the ICU Requiring Ventilatory Support: Results From a Prospective Multicenter Study. *By Dr. L. C. P. Azevedo et al.*

Macrolide/Azalide Therapy for Nodular/Bronchiectatic *Mycobacterium avium* Complex Lung Disease. *By Dr. R. J. Wallace Jr. et al.*

Cross-sectional Survey on Lobectomy Approach (X-SOLA). *By Dr. C. Cao et al.*

SPECIAL FEATURE: CDC PH SURVEILLANCE
Pulmonary Hypertension Surveillance: United States, 2001 to 2010. *By Dr. M. G. George et al.*

EVIDENCE-BASED MEDICINE
Pharmacologic Therapy for Pulmonary Arterial Hypertension in Adults: CHEST Guideline and Expert Panel Report. *By Dr. D. B. Taichman et al.*

EDITORIAL
Pulmonary Arterial Hypertension Treatment Guidelines: New Answers and Even More Questions. *By Dr. A. R. Hemnes.*

Citations on the rise, *CHEST* Journal makes huge Impact Factor jump

The release of the 2013 Journal Citation Reports (JCR) from the ISI Web of Knowledge proved to be great news for *CHEST*.

The journal's Impact Factor rose from 5.85 to 7.132, a significant 1-year jump. It is the highest Impact Factor in the history of the journal, and it moved *CHEST* into the rank of 2nd of 27 journals in the JCR Critical Care Medicine category, and moved *CHEST* to the rank of 3rd of 53 journals in the JCR Respiratory Systems category. These are also the highest rankings *CHEST* has held in each category.

Additional metrics also moved *CHEST* up. In the Eigenfactor (which eliminates potential bias of self-citations), as well as in Total Citations, *CHEST* now ranks 2nd in both the Critical Care Medicine and the Respiratory Systems categories.

In the metric of Current Articles, *CHEST* ranks 1st in the Critical Care Medicine category and 3rd in the Respiratory Systems category.

Because the Impact Factor is calculated by taking the total citations in the 2013 year to articles published in the previous 2 years, and dividing by the number of current articles published in the previous 2 years, the fact that *CHEST* ranks so highly in the denominator is testament to its impact overall.

Here's the formula:

A = the number of times that all items published in that journal in 2011 and 2012, were cited by indexed publications during 2013.

B = the total number of "citable items" published by that journal in 2011 and 2012. ("Citable items" for this calculation are usually articles, reviews, proceedings, or notes; not editorials or letters to the editor, and are called "current articles" in the JCR data).

2013 impact factor = A/B.

PULMONARY PERSPECTIVES: Necessary answers on endobronchial ultrasound of the mediastinum in NSCLC

BY DR. BALAJI LAXMANAN AND DR. SEPTIMIU MURGU, FCCP

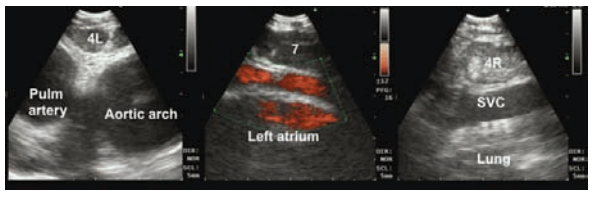
According to the current evidence-based CHEST lung cancer guidelines, patients with a high suspicion of N2 or N3 lymph node involvement, either by discrete nodal enlargement or PET uptake (and no distant metastases), endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA), endoscopic ultrasound needle aspiration (EUS-NA), or the combination of EBUS/EUS-NA is recommended over surgical staging as a best first test. For patients with an intermediate suspicion of N2 or N3 involvement defined as a radiographically normal mediastinum with a central tumor or N1 lymph node involvement (and no distant metastases), the same needle techniques are suggested (Silvestri et al. *Chest*. 2013;143(5 Suppl):e211S). The purpose of this essay is to address two questions pertinent to endosonographic staging of the mediastinum.

DR. LAXMANAN

DR. MURGU

1. Is it necessary to add EUS to EBUS for accurate staging of the mediastinum?

One trial randomized 241 patients to surgical staging alone or combined EBUS/EUS followed by surgical staging if endosonography was negative (Annema et al. *JAMA*. 2010;304[20]:2245). Sensitivities of 79%, 85%, and 94% were found for surgical staging, EBUS/EUS, and EBUS/EUS followed by surgical staging, respectively, when compared to the results obtained at surgical resection. This suggests the addition of EUS to EBUS increases the sensitivity of endosonographic staging. Another prospective study of 153 patients with confirmed or suspected NSCLC compared staging with EBUS-TBNA and cervical mediastinoscopy to lymph node sampling at the time of surgical resection (Yasufuku et al. *J Thorac Cardiovasc Surg*. 2011;142[6]:1393). EBUS-TBNA had a sensitivity of 81% compared with 79% for mediastinoscopy. Specificity for both techniques was 100%. This trial highlights the accuracy of EBUS, which was similar to mediastinoscopy.



ACCP

Commonly sampled mediastinal lymph nodes (from left): Station 4L, station 7, and station 4R.

Via EUS, however, one can reliably sample the left paratracheal (2L, 4L), subcarinal (7), and inferior mediastinal (8, 9) lymph nodes and variably visualize the aortopulmonary (AP) zone nodes (5, 6). For anatomical reasons, access to the right paratracheal lymph nodes (2R, 4R) is limited.

Given the ability to provide a minimally invasive evaluation of lymph node stations inaccessible by EBUS-TBNA, the addition of EUS to EBUS is an attractive solution for a more complete evaluation of the mediastinum. One might expect an increased sensitivity of combined EBUS/EUS due to the ability to sample lymph nodes not accessible by EBUS, particularly the inferior mediastinum. In an often cited study (Wallace et al. *JAMA*. 2008;299[5]:540), 138 patients with NSCLC underwent traditional TBNA, EBUS, and EUS in a single setting. The sensitivity for identifying malignant lymph nodes was 69% for EBUS and 93% for the combined EBUS/EUS procedure. No positive lymph nodes, however, were identified at stations 8 and 9, but EUS better identified malignant disease in stations 5, 6, and 7. In another trial (Hwangbo et al. *Chest*. 2010;138[4]:795), 150 patients with NSCLC underwent EBUS and EUS in the same procedure using the bronchoscope rather than an EUS endoscope. In the majority of cases, EUS-NA was performed due to better visualization of lymph nodes by EUS or inability to access the nodes by EBUS. Overall, EBUS had a sensitivity of 85% while the combined procedure increased the sensitivity to 92%. The lymph nodes diagnosed by EUS and missed by EBUS, however, were not located in the inferior mediastinum (8, 9) but at stations 4L and 5. In summary, the published evidence suggests that the addition of EUS to EBUS increases the sensitivity for evaluating the mediastinal lymph nodes in NSCLC. However, this increased sensitivity is not due to its ability to evaluate the inferior mediastinum but rather better characterization of the left paratracheal (4L) and subcarinal (7) lymph nodes and, in some patients, the ability to access the AP zone nodes.

The current guidelines recommend sampling the AP zone nodes by VATS, extended cervical mediastinoscopy, or Chamberlain procedure and not by EUS. In particular, patients with left-upper-lobe tumors and a negative invasive evaluation of the other mediastinal lymph nodes (assuming it is indicated as described above) should undergo biopsy of the AP zone nodes. As for the inferior mediastinal stations, recent evidence suggests that it is extremely rare for stations 8 and 9 to be involved without concurrent involvement of upper mediastinal nodes (2, 4, 7). In one study (Obiols et al. *Ann Thorac Surg*. 2014;97[3]:957), 621 patients underwent staging according to the European Society of Thoracic Surgeons guidelines. Unsuspected N2 disease was found in 30 patients, but in only 1 was this due to involvement in the inferior mediastinum (station 8), a rate of only 0.16%. This extremely low rate does not justify the routine exploration of the inferior mediastinum if the radiographic evaluation is negative and the superior mediastinal lymph nodes are uninvolved.

Therefore, based on the current published data, the benefit of adding EUS to EBUS as part of the endosonographic staging of the mediastinum occurs when sampling of the following stations affects staging and: (1) EBUS specimens from stations 4L and 7 are nondiagnostic or when these stations were unable to be sampled via EBUS; (2) stations 8 or 9 show CT- or PET-positive nodes; and (3) station 5 and 6 nodes are enlarged and deemed accessible by EUS.

2. Is EBUS assessment of the mediastinal and hilar nodes necessary prior to stereotactic radiosurgery?

Because of the very low prevalence of unsuspected pN2 disease in patients with peripheral clinical stage IA tumors (ie, negative mediastinal and hilar lymph nodes by CT and PET), guidelines suggest that invasive preoperative evaluation of the mediastinum is not required. For patients with inoperable stage I NSCLC, stereotactic body radiation therapy (SBRT), aka stereotactic ablative radiotherapy (SABR), has been used to deliver extremely high doses of localized radiation to the tumor while avoiding the toxicity of radiation to the surrounding normal tissue.

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EBUS is recommended for all stereotactic radiosurgery candidates.

Several studies have demonstrated the efficacy of SBRT for early stage NSCLC, with primary tumor control rates of greater than 90%. The results of a trial of 55 patients, medically inoperable, with T1/2N0MO NSCLC undergoing SBRT (Timmerman et al. *JAMA*. 2010;303[11]:1070) demonstrated a 3-year primary tumor control rate of 97.6%. The rate of loco-regional control, however, was 87.2%, and the rate of distant failures was 22.1%. Another trial (Onishi et al. *Int J Radiat Oncol Biol Phys*. 2011;81[5]:1352) retrospectively evaluated the results of SBRT performed on 87 patients with stage I NSCLC who were surgical candidates but refused resection. At 5 years, the local control rate was 92%, and the regional lymph node and distant metastases-free rates were 85.3% and 75.1%, respectively. This pattern of recurrence with a significant number of patients presenting with regional and distant failure is further supported by a large retrospective series of patients undergoing SBRT (Senthi et al. *Lancet Oncol*. 2012;13[8]:802).

Regional recurrence (ie, nodal disease) occurs in approximately 15% of patients treated with SBRT (Kilburn et al. *J Thorac Oncol*. 2014;9[4]:572). This may be due to the fact that these patients, who are usually medically inoperable, are staged by CT and PET but not invasively as is the standard of care for surgical candidates (Grills et al. *J Clin Oncol*. 2010;28[6]:928). Furthermore, even in patients who have undergone curative intent surgical resection, unsuspected disease

Continued on following page

Got specificity? Test your ICD-10-CM coding skills

BY RHONDA BUCKHOLTZ, CPC, CPMA, CPC-I, CENTC, CGSC, COBGC, CPEDC
Vice President of ICD-10 Training and Education at AAPC

When preparing for chest coding in ICD-10-CM, it is best to walk through real cases to help you strengthen areas that will affect your practice the most. To see if you document with enough clinical specificity, here is a snapshot of chest coding using ICD-10-CM:

▶ **History of present illness:** The patient is a 65-year-old woman who underwent left upper lobectomy for stage IA non-small cell lung cancer. She returns for a routine surveillance visit.

Since her last visit, she has undergone an abdominopelvic CT, which was normal. She underwent barium swallow, which demonstrates a small sliding hiatal hernia with minimal reflux. She has a minimal delayed emptying secondary tertiary contractions. Posteroanterior (PA) and lateral chest radiographs from 11/23/09 were also reviewed, which demonstrate no lesions or infiltrates. The patient continues to have periodic odynophagia and midthoracic dysphagia. She denies weight loss, anorexia, fevers, chills, headaches, new aches or pains, cough, hemoptysis, shortness of breath at rest, or dyspnea on exertion.

▶ **Physical examination:** BP: 117/78, RR: 18, P: 93
Wt: 186 lbs. room air saturation: 100%. HEENT: Mucous membranes are moist. No cervical or supraclavicular lymphadenopathy. Lungs: Clear to auscultation bilaterally. Cardiac: Regular rate and rhythm without murmurs. Extremeties: No cyanosis, clubbing, or edema. Neuro: Alert and oriented x3. Cranial nerves II through XII intact.

▶ **Assessment:** Patient is here for surveillance with history of lung cancer and no evidence of disease now. Status post-left upper lobectomy for stage IA non-small cell lung cancer 13 months ago.

▶ **Plan:** She is to return to clinic in 6 months with a chest CT. She will be called with the results. She was given a prescription for nifedipine 10 mg by mouth three times daily as needed for esophageal spasm.

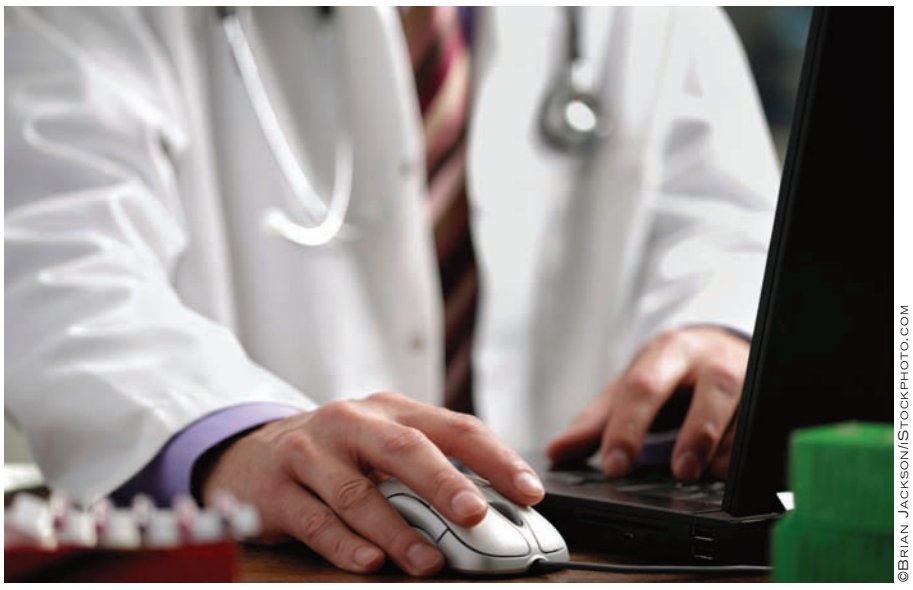
ICD-10-CM code(s):

Z08 *Encounter for follow-up examination after completed treatment for malignant neoplasm*

Z90.2 *Acquired absence of lung (part of)*

Z85.118 *Personal history of other malignant neoplasm of bronchus and lung*

▶ **Rationale:** This example states the patient presented for a surveillance visit with a history of lung cancer. Under code Z08, there are two instructional notes that indicate other codes and their sequencing. The first one states to use an additional code to identify any acquired absence of organs. This patient had a left upper lobectomy, so the second listed code is the absence of the lung. The next instructional note states to use an additional code to identify the personal history of malignant neoplasm, in this case the lung. According to the ICD-10-CM guidelines (I.C.2d), when a primary malignancy has been previously excised or eradicated from its site and there is no further treatment directed to that site and no evidence of any existing primary malignancy, a code from **Z85**, *Personal history of malignant neoplasm,* should be used to indicate the former site of the malignancy.



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Beef up your coding prowess with this test drive of a case of a 65-year-old woman who underwent a lobectomy for stage IA NSCLC.

Continued from previous page

in the mediastinum is a relatively common finding. In a recent study (Obiols et al. *Ann Thorac Surg.* 2014;97[3]:957), unsuspected N2 disease was noted in 10/134 (7.5%) patients taken for resection despite a negative staging evaluation by CT and PET. As lymph node sampling or dissection is a routine part of any surgical resection, unsuspected N1 or N2 disease will become evident. Therefore, committing patients with peripheral clinical stage IA tumors directly to thoracotomy may still be an appropriate strategy. However, it is less appropriate for patients who are referred for SBRT. For these patients, definitive pathologic evaluation of the lymph nodes does not occur. Therefore, patients with unsuspected N1 or N2 disease receive suboptimal treatment, as they would otherwise have been referred for adjuvant chemotherapy after surgical resection or definitive chemo-radiation rather than SBRT. In a retrospective study, 59 consecutive patients with negative radiographic staging and considered candidates for SBRT underwent bronchoscopic fiducial marker placement. All patients also underwent EBUS, and malignant involvement of mediastinal lymph nodes was noted in 16% of cases (Sarwate et al. *J Thorac Cardiovasc Surg.* 2012;144[1]:81).

These retrospective data and current staging strategies suggest that EBUS-TBNA is more accurate than CT and PET and less invasive than mediastinoscopy. Therefore, until more data become available, EBUS should be performed in all patients who are candidates for stereotactic radiosurgery.

A prospective study is currently testing whether there is a difference in accuracy between CT/PET and EBUS-TBNA for mediastinal staging in patients with NSCLC prior to SBRT (clinicaltrials.gov/show/NCT01786590).

Drs. Laxmanan and Murgu are with the Division of Pulmonary and Critical Care, University of Chicago, in Illinois.

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FRONTLINE MEDICAL COMMUNICATIONS

CHEST releases updated PAH guideline

Resource offers 79 management recommendations.

BY DR. DAVID BADESCH, FCCP

Recently, the American College of Chest Physicians (CHEST) announced the release of the Online First publication of *Pharmacological Therapy for Pulmonary Arterial Hypertension in Adults: CHEST Guideline* in the journal *CHEST*. Previous iterations of the guidelines were published in 2004 and 2007. The new guidelines provide recommendations to help clinicians manage PAH using the latest therapies.

The distance traveled in the management of PAH during the past 2 decades has been impressive.

DR. BADESCH

Pulmonary arterial hypertension (PAH) can strike anyone, but individuals with connective tissue diseases, such as scleroderma, liver disease, or HIV infection, are more likely than the general population to have PAH. Prompt recognition and referral to an expert center for accurate diagnosis and appropriate treatment remain cornerstones of optimal management.

The CHEST guideline represents an authoritative and useful resource about where pharmacologic therapy for PAH stands in 2014 and where knowledge gaps in evidence remain. The guideline is intended to be a "living document," regularly updated as new evidence becomes available.

Despite recent growth in therapeutic options, questions remain regarding pharmacologic treatments. *Pharmacological Therapy for Pulmonary Arterial Hypertension in Adults: CHEST Guideline* contains 79 recommendations and expert consensus statements to aid clinicians in the management of PAH using the latest drug therapies for adults with the condition.

The guideline is intended to be a 'living document,' regularly updated as new evidence becomes available.

The methodology used in the development of this guideline is rigorous, and each recommendation was derived from a transparent process. While the evidence that supports some recommendations is robust, the guideline also serves to highlight the areas in which the evidence base, unfortunately, remains less than adequate. There is no question that the distance traveled in the management of PAH during the past 2 decades has been impressive and, indeed, has exceeded that in most other branches of pulmonary medicine. But, the ultimate destination of ideal therapies supported by rigorous, robust evidence still lies ahead.

Dr. Badesch is the Director of the Pulmonary Hypertension Program at the University of Colorado. He is a Past-Chair of the Scientific Leadership Council of the Pulmonary Hypertension Association (PHA), as well as a Past-Chair of the Pulmonary Circulation Assembly of the American Thoracic Society (ATS). Dr. Badesch helped to lead the writing group developing the Medical Therapy Guidelines published by the American College of Chest Physician's (CHEST) Consensus Panel in 2004 and the Update to the Medical Therapy Guidelines published in 2007.

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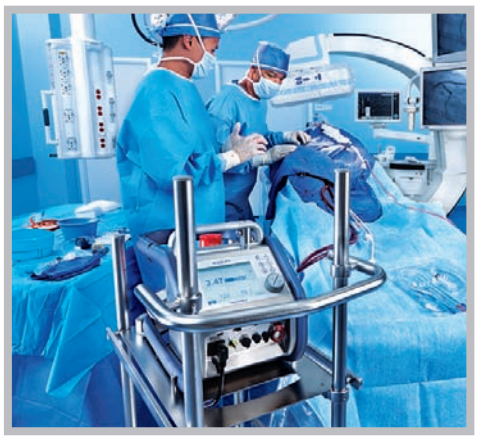

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