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THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

CRITICAL CARE COMMENTARY

PHOTO COURTESY OF CHEST

"The ICU is where palliative care may have the greatest impact in a hospital," Dr. Earl L. Smith and Dr. Tita Castor explain in this month's Critical Care Commentary, page 30.

PULMONARY PERSPECTIVES

Procedures in the ICU – Don't let them slip away

BY DR. NICHOLAS J. PASTIS, FCCP; AND DR. GERARD A. SILVESTRI, FCCP

As pulmonary/critical care becomes more complex and demands on our time increase, many argue that we should not take on additional time and potential liability for procedures in the ICU. In some institutions, pulmonary/critical care physicians are not credentialed to perform tube thoracostomy or endotracheal tube intubation due to local culture, lack of training, or hospital policies. When credentialing for such procedures is based upon specialty alone rather than competence, procedural "ownership" may occur, whereby barriers to care,

See **Pulmonary Perspectives** • *page 12*

Sepsis resuscitation reduces mortality, even after 6 hours

Better late then never for bundle goals.

BY SHERRY BOSCHERT
Frontline Medical News

SAN FRANCISCO – Meeting the goals of the Surviving Sepsis Campaign's resuscitation care bundle significantly decreased the risk for in-hospital mortality, even when the goals were met beyond the recommended 6-hour window after diagnosis of severe sepsis, a study of 395 patients found.

In-hospital mortality rates were 88% lower in the 85 patients who met the resuscitation bundle goals 6-18 hours after diagnosis and 55% lower in the 95 patients who met the goals within the desired 6 hours after diagnosis compared with 216 patients who did not reach the goals within 18 hours of diagnosis, Dr. Zerihun A. Bunaye reported at the Critical Care Congress, sponsored by the Society for Critical Care Medicine.

For resuscitation care in severe sepsis, it's better late than never, he said. "Definitely this is showing that there's a benefit if we continue to aggressively resuscitate the patients beyond 6 hours and try to achieve the goals," said Dr. Bunaye of Mercy Hospital, St. Louis. The lead investi-

See **Sepsis** • *page 10*

INSIDE

Best to test drive your ICD-10 prep. Now!

BY MARY ELLEN SCHNEIDER
Frontline Medical News

Still not prepared for the switch over to ICD-10? Experts say there's still time to catch up before the Oct. 1 compliance date.

In an ideal world, physicians, their coders, and office staff would have already fully assessed the cost of transitioning to ICD-10, would have undergone training about how to improve clinical documentation and appropriate use of the new diagnosis codes, and would have internally tested their upgraded software. That would leave more than half a year to complete external testing with health plans to ensure that they get paid in October.

The reality? Few are on

See **Coding** • *page 6*

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Safety interventions haven't dented adverse event rate

BY ALICIA AULT
Frontline Medical News

Adverse events increased for Medicare inpatients with pneumonia or conditions requiring surgery, despite recent focus on prevention, according to an analysis of a Medicare database.

While researchers noted a decrease in adverse events among acute myocardial infarction (AMI) or heart failure (HF) patients, they also found that concerted efforts to improve patient safety were not necessarily broadly effective: There was an increase in pressure ulcers in postsurgical patients, and no decline in ventilator-associated pneumonia in most patients, even though there have been initiatives focused on those conditions, Yun Wang, Ph.D., of the Harvard School of Public Health, Boston, and his colleagues found.

"Our finding of an increased adverse-event rate among surgical patients indicates a continuing challenge and identifies an important target for patient-safety initiatives," the researchers wrote in the New England Journal of Medicine.

The researchers examined whether hospitalized patients are any better off in light of the current focus on patient safety, including the launch of initiatives such as the American College of Surgeons' National Surgical Quality Improvement Program and the federal government's Surgical Infection Prevention Project.

Investigators used three composite outcomes measures: the rate of occurrence for adverse events for which patients were at risk (for instance, only patients receiving warfarin were at risk for warfarin-related events); the proportion of patients with one or more adverse events; and the number of adverse events per 1,000 hospitalizations. They analyzed data on 61,523 patients who were discharged from 4,372 hospitals; the data were extracted from the Medicare Patient Safety Monitoring System database (N. Engl. J. Med. 2014:370;341-51).

The 61,523 patients included 11,399 with AMI, 15,374 with HF, 18,269 with pneumonia, and 16,481 with conditions requiring surgery. Postsurgical patients largely were being treated for joint replacement procedures and other osteoarthritis-related conditions, femur fracture, colon cancer, post-AMI procedures, or other forms of chronic ischemic heart disease.

Postsurgical patients experienced slight increases in all three outcomes measures, in particular, increases in infection-related and postprocedural events such as venous thromboembolism, and cardiac and catheter-related events. The number of events per 1,000 hospitalizations for pneumonia patients increased insignificantly from 216 to 223. For postsurgical patients, the number of events increased insignificantly from 352/1,000 to 368/1,000.

Infection-related and drug-related adverse events declined significantly in heart attack and HF patients. There was also a substantial improvement in postprocedure events in HF patients. The improvements likely translated to 81,000 fewer adverse events for patients with AMI and HF from 2010 to 2011 alone, according to the study.

From 2005-2006 to 2010-2011, AMI and HF patients saw a 1.3–percentage point decline in the rate of adverse events, from 5% to 3.7%. The proportion who had one or more such events decreased from 26% to 19%. The number of adverse events per 1,000 hospitalizations declined from 402 to 262 for AMI patients and from 235 to 167 for HF patients.

There was no decline in ventilator-associated pneumonia in most patients, even though there have been initiatives focused on the condition.

Patients who had adverse events had significantly longer hospital stays and were at higher risk for death. As the number of adverse events increased, so did the risk of death.

"Although this suggests that national efforts focused on patient safety have made some inroads, the lack of reductions across the board is disappointing," the researchers wrote.

The study was supported by the Agency for Healthcare Research and Quality as well as academic and federal grants. Several researchers were associated with Qualidigm, a consultancy that administers the Medicare database. No other relevant conflicts of interest were disclosed.

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IN THIS ISSUE

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

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Opsumit®

macitentan tablets 10 mg

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

ACTELION

Opsumit®
macitentan tablets 10 mg

Rx only

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

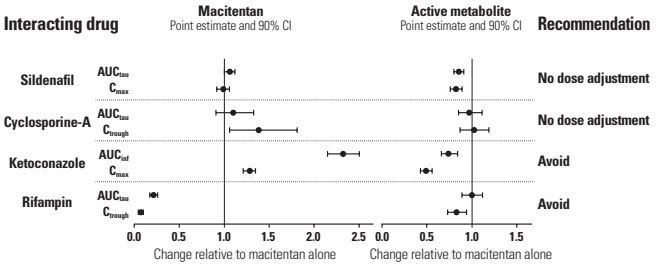
In vitro studies

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

ACTELION

Take ICD-10 prep for a test drive

Coding *from page 1*

track to meet those milestones on time.

"Everybody is behind, not just practices," said Robert Tennant, senior policy adviser at the Medical Group Management Association (MGMA). For a practice to be ready for ICD-10, the "key trading partners have to be ready and our surveys are indicating that they are not," he said.

Those partners include practice management software vendors, electronic health record (EHR) vendors, clearinghouses, and private and public payers.

So does that mean another ICD-10 delay is likely? The Centers for Medicare & Medicaid Services says no.

Part of the reason may be that health plans, which are investing money in upgrading their own systems, are pushing the agency to move forward on time. They are signaling to the government that they don't want another delay, Mr. Tennant said.

The MGMA is advising its members to prepare for an Oct. 1 launch of ICD-10. But Mr. Tennant said he's not entirely convinced that the CMS will stick to the date if much of the health care industry is unprepared to make the switch.

"Claims have to be paid," he said. "The system cannot grind to a halt because practices that aren't paid can't see patients."

Start with training

Assuming that most physician offices have assessed which parts of their practice management and EHR systems need to be upgraded, and have determined the cost for upgrades and training, it's time to get familiar with the new diagnosis coding system.

Management software vendors and EHR firms are not yet ready. 'Everybody is behind, not just practices.'

MR. TENNANT

Coders and billers will need the most training on the new coding methodology, but doctors still need to get familiar with the level of documentation that's needed for their most frequently used codes. In general, the new system calls for great specificity, though it's not an absolute rule.

For instance, the classification for asthma has changed from ICD-9 to ICD-10. Physicians will need to provide more specific documentation about the severity level (moderately persistent, severely persistent, etc.) for their coders to select the appropriate ICD-10 code, according to Kathryn DeVault, a coding expert at the American Health Information Management Association (AHIMA).

"The good news is that as different as ICD-10 and ICD-9 are, they are similar," Ms. DeVault said. "If there's a familiarity or comfort level working with ICD-9, it's a natural transition to ICD-10."

While there are some significant changes, especially related to orthopedic codes, for many subspecialties the differences will be minimal, she said.

Ms. DeVault recommended having the practice manager or lead coder identify the top 20 diagnosis codes for every physician in the practice and build some education around those frequently used codes.

She cautioned doctors not to skimp on the time and money needed to thoroughly train themselves and their staffs. "The key here is to do it right and do it right the first time," she said.

Check the books

Physicians and their staff also need to evaluate their current cash flow and revenue cycle, including the age of account balances, billing lag time, and other issues that may result in delayed or denied claims, said Asia Blunt, practice management strategist at the American Academy of Family Physicians. Correct those problems now, she said, then reevaluate between April and August.

Experts at the AAFP are recommending that physicians put aside a cash reserve, if possible, to cover expenses during the first 3 months of the transition in case large numbers of claims are denied. (See box at left for more tips on planning for the worst.)

Test with vendors, payers

Internal and external testing is also key. Before Oct. 1, practices should have completed end-to-end testing of their upgraded systems, ensuring that everything works smoothly from the time they code a claim to when they receive payment from the health insurer.

Practices can begin internal testing as soon as they have upgraded their software. But external testing will depend on when clearinghouses and health plans are ready.

The CMS will provide the first testing opportunity March 3-7. The agency will hold a national ICD-10 testing week allowing practices and clearinghouses to submit claims using the new coding system.

Practices will receive an acknowledgement that the claims were either accepted or rejected by the system. Practices must register in advance through their local Medicare Administrative Contractor (MAC) website to test. (Locate your local MAC at tinyurl.com/FindmyMAC.)

But this type of front-end testing is only a first step, Mr. Tennant said. Front-end testing determines whether the claim contains an ICD-10 code and if it is in the right place and the right format. But practices will need to conduct further testing with payers to determine if the code they used is appropriate and whether they will get paid.

Each health insurer has different coding policies and those policies have yet to be released for ICD-10.

"It's very frustrating for everybody," Mr. Tennant said.

To minimize the impact, Mr. Tennant recommended identifying the payers responsible for the majority of your claims. Keep in contact with them about the release of their payment policies and testing schedules, he said.

"Be aggressive in your outreach to those plans," he said.

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Got a backup plan?

Just in case a worst-case scenario develops, Mr. Tennant offered the advice on ICD-10 contingency plans:

► Research back-up options for practice management systems and clearinghouses. If the vendors aren't providing a clear answer on when they will be ready to offer upgrades and testing, start researching alternatives. Ask colleagues if they have vendors that are prepared for the transition.

► Don't rely on one coder. Train more than one staff member on how to use the new coding system. That way, if the chief coder leaves 3 weeks before the compliance date, someone else can step in.

► Limit vacations around the Oct. 1 compliance date. This is not a time to operate short staffed.

► Don't wait around for health plans to start ICD-10 testing. Start with context testing. Take a subset of high-dollar, high-volume ICD-9 claims that have already been paid by the health plan and practice coding them in ICD-10. Similarly, begin to code claims in parallel in both ICD-9 and ICD-10 and move them through your internal workflow. In both of these testing approaches, check if the documentation provided is sufficient to identify the best ICD-10 code. If not, it's time for more training.

► Ensure you have enough cash to operate in case claims are rejected or delayed. Setting aside cash reserves is a good move. Consider postponing major capital investments for a few months before and after Oct. 1. Obtaining a line of credit to cover a few months of operating expenses is another option.

► Submit as many of claims as possible with ICD-9 codes before Oct. 1.

Free resources and tools online

► The Centers for Medicare & Medicaid Services (CMS) provides a guide with checklists and timelines at tinyurl.com/CMS-ICD10resources.

► The American Health Information Management Association offers a sample letter to gauge vendors' ICD-10 readiness. Find the document in the AHIMA library at tinyurl.com/Sample-ICD10Letter.

► From the American College of Cardiology comes "ICD-10: What You Need to Know." Find it at cardiosource.org/practice-management/coding-and-billing/ICD10.aspx.

► The American Medical Association offers a 12-step transition plan, white papers, and a practice tool on its website in exchange for your filling out a form with your contact information. Find the resources here: tinyurl.com/AMA-ICD10tools.

CMS to release individual physician payment data

BY MARY ELLEN SCHNEIDER
Frontline Medical News

Reversing more than 30 years of policy, federal officials announced they would soon begin releasing data on how much Medicare pays to individual physicians.

Officials at the Centers for Medicare & Medicaid Services (CMS) announced Jan. 14 that they would take a "case-by-case" approach to the release of individual physician payment information, weighing the right for privacy against the value to the public in each Freedom of Information Act request they receive.

'We intend to consider the importance of protecting physicians' privacy.'

MR. BLUM

In addition to fielding individual requests for physician data, the agency plans to generate and publish aggregate data sets on physician services.

The policy change will take effect on March 18.

"As CMS makes a determination about how and when to disclose any information on a physician's Medicare payment, we intend to consider the importance of protecting physicians' privacy and ensuring the accuracy of any data released as well as appropriate protections to limit potential misuse of the information," Jonathan Blum, CMS Principal Deputy Administrator, wrote in a blog post on Jan. 14.

Last May, a federal judge cleared the way for this policy shift by lifting an injunction that had barred the agency from making public its database of Medicare physician claims.

The new policy has plenty of benefits, Mr. Blum wrote, including allowing providers to collaborate on better care management, giving consumers more reliable measures of quality and performance, and allowing journalists and researchers to identify Medicare waste, fraud, and abuse.

The change is also part of a broader effort at the CMS to make health care prices more transparent.

Physicians' groups have been urging caution as the CMS evaluated the release of physician data. In a Sept. 5 letter signed by the American Medical Association as well as several specialty and state medical societies, physicians said that the CMS must educate the public about the limitations of analyzing Medicare claims data. For example, Medicare claims may not include many factors that influence the cost of medical care, including specialty, location, patient mix, other demographics, and practice costs.

In the letter, the physician organizations urged the CMS to provide access to data to organizations that have experience in handling and analyzing Medicare data. And they called for the opportunity to review and correct their information in a timely manner.

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What to do about indeterminate pulmonary nodules

BY DOUG BRUNK
Frontline Medical News

SAN DIEGO – About 30% of nodules detected by CT screening fit the criteria for an indeterminate pulmonary nodule. Very few of those nodules represent cancer, and the question is, what do you recommend for those patients in terms of follow-up?

"We're encountering more and more patients with lung nodules in the clinic, and with the advance of screening, it will become even more of a problem. The numbers are tremendous," Dr. Pierre P. Massion stated at the Joint Conference on the Molecular Origins of Lung Cancer, sponsored by the American Association for Cancer Research and the International Association for the Study of Lung Cancer.

Dr. Massion, the Ingram Professor of Cancer Research at Vanderbilt-Ingram Cancer Center in Nashville, Tenn., said it's important to differentiate – early, accurately, and noninvasively – benign lesions from cancer. "There is a race for early diagnosis, because surgery is the best chance for cure … but we also need to decrease the number of thoracotomies performed for benign disease."

Data from eight large trials of lung cancer screening examined the relationship between lesion size and the probability of lung cancer (Chest 2007;132[3 Suppl]:94S-107S).

We need to decrease the number of thoracotomies performed for benign disease.

DR. MASSION

The probability of cancer was 0%-1% for lesions less than 5 mm in diameter; 6%-28% for those 5-10 mm, 33%-60% for those 11-20 mm, and 64%-82% for those 21-30 mm.

"The bigger the nodule, the greater the probability of cancer. In fact, however, the number of large nodules is very small," Dr. Massion said. "The indeterminate ones are between 5 and 15 mm in diameter, and these are the ones we struggle with how best to handle." The probability of cancer from indeterminate pulmonary nodules ranges from 6% to 60%, which is a large range.

The shape of the nodule provides additional information, Dr. Massion said. Triangular shape abutting a fissure and central calcification are generally indicators of benign disease and typically do not require follow-up. Alternatively, solid, noncalcified spiculated nodules have a high likelihood of being cancer. Part solid nodules are "very worrisome," he said.

"These are most likely to contain malignancy. Nonsolid lesions, also called ground-glass opacities, are troublesome and difficult to assess. They represent about a 20% probability of disease."

The rate of growth of small nod-

Continued on following page

Continued from previous page

ules over time "is probably one of the best imaging markers, [but] for small nodules such as those 5 mm in diameter, the volumetric analysis has a large coefficient of variance," he said.

Prediction models are important to the evaluation of lung nodules, yet even with existing tools "we're wrong about 30% of the time," he said. The best three prediction models come from studies of patients at the Mayo Clinic (Arch. Intern. Med. 1997;157:849-55) and the Veterans Affairs department (Chest 2007;131:383-8), and from those enrolled in the PLCO (Prostate, Lung, Colorectal, and Ovarian) Cancer Screening Trial (N. Engl. J. Med. 2013;368:728-36). These prediction models are now recommended for use on nodules greater than 8 mm in diameter in the ACCP 2013 guidelines for evaluation of lung nodules (Chest 2013;143[5 Suppl]:e93S-120S).

"We have no models for never-smokers, which is a huge problem in the community at the moment."

Dr. Massion predicted that serum biomarkers might "come to the rescue" for deciding which patients with indeterminate pulmonary nodules might need to go for a biopsy or resection and which can be carefully watched over time.

In a separate study of 62 lung nodules that integrated clinical, imaging, and protein biomarker findings, clinical information alone resulted in about 50% sensitivity for predicting disease, "which is not great," said Dr. Massion, who was the principal investigator (Cancer Epidemiol. Biomarkers Prev. 2012;21:786-92). The addition of CT imaging increased the area under the curve to about 61%. Adding biomarkers in the blood raised the bar to about 69%.

"It's not a panacea, but we show a trend toward improvement of classification of these nodules, which is where I think this field is going – integrating information from the clinic, imaging, and the discriminatory power of biomarkers," Dr. Maisson noted.

Dr. Massion said that he had no relevant financial conflicts to disclose.

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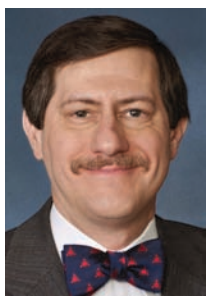
VIEW ON THE NEWS

Dr. Frank Podbielski, FCCP, comments: It is clear that timely intervention in early-stage lung cancer saves lives. Discrimination of nodules by size and shape aids in stratification of risk for cancer, but falls short in terms of cost-effectiveness for mass screening programs. The classic dilemma lies in the 6-mm lung nodule/cancer with an extremely slow growth behavior, below the level of PET resolution, difficult to biopsy percutaneously or via VATS, and out of reach of navigational bronchoscopy.



Even with specific biomarkers, one can envision an infinitesimally low plasma concentration of a biomarker secreted from a 3-mm tumor in an 80-kg adult. Clearly, more work and new, novel diagnostic strategies are required.

Data suggest better late than never

Sepsis *from page 1*

gator in the study was Dr. Farid Sadaka, also of the hospital.

Better survival in the group that complied with resuscitation bundle goals in 6-18 hours compared with the 6-hour compliance group surprised the investigators and may be due to several confounding factors that were not analyzed in the study, he said.

The Surviving Sepsis Campaign recommends two sets of "bundles" of care (sets of elements of care selected from evidence-based practice guidelines that have an effect on outcomes when implemented as a group that's beyond the effect of individual implementation), some to be completed within 3 hours and other goals to be met within 6 hours.

The resuscitation bundle of care aims to prescribe appropriate antibiotics within 3 hours.

DR. BUNAYE

The resuscitation bundle of care aims to prescribe appropriate antibiotics within 3 hours and within 6 hours to get the patient's mean arterial pressure above 65 mm Hg, get central venous pressure above 8 mm Hg, achieve central venous oxygen saturation greater than 70%, and measure lactic acid, Dr. Bunaye said.

The investigators prospectively collected data as part of a performance improvement project with feedback mechanisms for alerting physicians when bundle goals were not being met so they could continue efforts to meet the goals beyond the recommended deadlines.

The study included patients with septic shock treated between July 2011 and January 2013 in a 54-bed ICU at the large university-affiliated hospital. It compared compliance with the resuscitation bundles within 18 hours of diagnosis and survival rates during approximately 31 days in the hospital.

Compared with the 54% of cases that did not comply with the resuscitation bundles within 18 hours, the hazard ratio for mortality was 0.45 in the 24% of cases that complied within 6 hours and 0.12 in the 22% that complied within 18 hours, Dr. Bunaye reported. Patients in the three groups did not differ significantly at baseline by age, weight, or Sequential Organ Failure Assess-

ment score.

Previous studies have suggested that only 30%-40% of hospitals adhere to the Surviving Sepsis Campaign guidelines. The current study suggests that continuing efforts to meet the goals beyond 6 hours are beneficial, he said.

The findings are limited by the small sample size and the focus on a single institution. The study also did not account for potential confounding variables.

'Definitely this is showing that there's a benefit if we continue to aggressively resuscitate the patients beyond 6 hours and try to achieve the goals.'

Severe sepsis in the United States is more common than AIDS, colon cancer, and breast cancer combined and is the leading cause of death in noncoronary ICUs, the literature suggests. The United States sees more than 500,000 cases of severe sepsis and septic shock each year, leading to death in 20% of patients with severe sepsis and 45% of those with septic shock, Dr. Bunaye said.

The investigators reported that they have no relevant financial disclosures.

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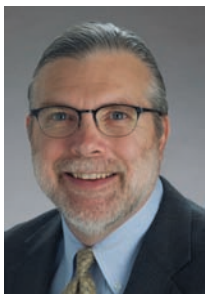
VIEW ON THE NEWS

Dr. Steven Q. Simpson, FCCP, comments: It is very encouraging to see that benefit accrues to patients who meet SSC (and National Quality Forum) bundle goals for physiological parameters, even if they are not met until later in the course of severe sepsis treatment. It seems a bit paradoxical that those who meet physiological goals between 6 and 16 hours after presentation have a higher mortality reduction than those who meet goals within 6 hours. Unfortunately, the study was not set up to determine how or why that may have happened, and whether the phenomenon is real.



The key point, though, is that these are valid goals to work toward in patients with severe sepsis and septic shock, and that we should follow through even when we miss the 6-hour time frame.

Hold on to procedures in the ICU

Pulmonary Perspectives *from page 1*

lack of collaboration, and duplication of services can occur (Kovitz et al. *Chest*. 2013;144[2]:368). We argue that by retaining procedural skills in the ICU, there are benefits to our patients and profession that should not be relinquished.

No other physician knows a patient and family as well as the intensivist in charge of their care. With such complete knowledge, issues such as fluid management, bleeding risk, sedative options, goals of care, and comorbidities can be factored into the planning and execution of procedures, thus preparing the physician to manage

No other physician knows a patient and family as well as the intensivist in charge of their care. Such complete knowledge can be factored into the planning and execution of procedures.

complications. A common conundrum occurs when we delegate procedures to other specialties, such as interventional radiology in which the ICU physician may be held hostage to international normalized ratio (INR) thresholds or platelet requirements that are not evidence-based or even achievable in some patients. The unnecessary or excess use of blood products may delay urgent procedures or even place patients at risk for transfusion reactions, acute lung injury, or infection. Sedation/analgesia choices used to facilitate procedures should be tailored to each critically ill patient, especially considering that excess use of certain sedatives in the ICU has been linked to worsened clinical outcomes and even long-term cognitive impairment (Miller et al. *Semin Respir Crit Care Med*. 2006;27[3]:210).

While some medical centers have surgical or airway teams on call when a chest tube or advanced airway is needed, many hospitals do not. Even in the ones that do, there may not be a guarantee of timely responsiveness (eg, emergent need for a chest tube or an airway when the surgeon or on-call anesthesiologist is preoccupied). Problems develop when the training of our country's critical care workforce occurs in environments that do not prepare them for conditions they will encounter following graduation. Without advanced training in lifesaving skills, such as airway management, potential harm to future patients may occur when that expertise is otherwise unavailable.

The American College of Chest Physicians has recommended against a 1-year critical care fellowship for internal medicine hospitalists to obtain board certification, with skill and experience in invasive procedures, and has argued for longer training (Baumann et al. *Chest*. 2012;142[1]:5). These skills include standard bronchoscopic procedures that are needed for emergent or urgent diagnostic or therapeutic purposes in the ICU. These procedures should be germane to graduates of pulmonary/critical care fellowships and include bronchoscopy with therapeutic suctioning that can relieve airway obstruction.They should also include BAL to diagnose alveolar hemorrhage, *Pneumocystis jiroveci* pneumonia (PJP), or acute eosinophilic pneumonia. Transbronchial needle aspiration (TBNA) can be used to diagnose treatable causes of respiratory failure, such as small cell lung cancer or lymphoma; transbronchial and endobronchial biopsies are used to diagnose malignant, inflammatory, and infectious processes.

DR. PASTIS

Unlike bronchoscopy requirements that are standardized for pulmonary fellowships, there is presently no specific number of endotracheal intubations that deem someone competent, and training in this skill varies widely across the United States (Joffe et al. *Respir Care*. 2012;57[7]:1084). As there are defined competency metrics for endotracheal tube intubation in emergency medicine, one can make a strong argument for the same in pulmonary/critical care. In fact, the American Board of Internal Medicine (ABIM) and the Accreditation Council for Graduate Medical Education (ACGME) require proficiency in emergent endotracheal intubation to graduate from pulmonary/critical care fellowships. Mayo and authors demonstrated that with proper training, which incorporates simulation, crew resource management, and adequate equipment (eg, video laryngoscope, bronchoscope, subglottic devices, etc), emergent endotracheal intubation may be performed safely by pulmonary/critical care medicine physicians (Mayo et al. *J Intensive Care Med*. 2011;26[1]:50).

It is a tremendous advantage for interventional pulmonologists or properly trained intensivists to perform percutaneous dilatational tracheostomies (PDT) in the ICU. Numerous studies document the comparable safety profile of PDT compared with surgical tracheostomy, along with decreased patient charge, increased efficiency, shorter procedure time, decreased bleeding, and decreased postoperative stomal infection rates (Yarmus et al. *Respiration*. 2012;84[2]:123). In addition, properly trained intensivists from nonsurgical specialties can perform PDT as safely as surgeons (Seder et al. *Neurocrit Care*. 2009;10[3]:264).

DR. SILVESTRI

The past decade has seen a new paradigm shift in the types of chest tubes placed in the ICU (Bauman et al. *Chest*. 2012;142[1]:536). It is no longer considered blasphemy to place smaller bore catheters (less than or equal to 14F) for most situations, including empyema (Rahman et al. *Chest*. 2010;137[3]:536) and most pneumothoraces (Lin et al. *Am J Emerg Med*. 2010;28[4]:466). Such tubes can be safely placed via a modified Seldinger technique and do not require surgical consultation or a radiologist. Even small collections can be safely drained under ultrasound guidance. With the use of deoxyribonuclease and tissue plasminogen activator through small-bore tubes, the drainage of complex pleural infections is improved and the frequency of surgeries and the duration of the hospital stay can be reduced (Najib and Rahman. *N Engl J Med*. 2011;365:518).

The role of thoracic ultrasound has been instrumental in the success of pleural procedures for the nonsurgeon, and in addition to directing placement in fluid collections, bedside ultrasonography is now standard of care for detecting pneumothorax in the ICU for those with proper training. Ultrasound can detect 92% of occult pneumothoraces diagnosed with CT scan (Soldati et al. *Chest*. 2008;133[1]:204). In addition, it is more sensitive than chest radiography and it allows for rapid reassessment (Galbois et al. *Chest*. 2010;138[3]:648). It can also be used to quickly rule out pneumothorax after central line placement or transbronchial biopsy (Vezzani et al. *Crit Care Med*. 2010; 38[2]:533).

For the pulmonary/critical care physician trained in point-of-care echocardiography, it no longer makes sense to wait on the official results of an echocardiogram for acutely ill patients. For the intensivist, bedside echocardiography has established itself as a powerful hemodynamic tool to diagnose and treat patients with hemodynamic failure. In a matter of minutes, a therapeutic plan can be initiated and results monitored. Volume responsiveness can be assessed and acted upon in most cases without additional invasive procedures (Mayo et al. *Chest*. 2009; 135[4]:1050).

In conclusion, diagnostic and therapeutic procedures should only be performed by those with adequate training and experience. The use of simulation (particularly for lower frequency, higher stakes procedures) and more evidence-based modalities for assessing competence are opportunities to ensure the highest level of skill in performing ICU procedures (Kennedy et al. *Crit Care Med*. 2014;42[1]:169). For many, the allure of the ICU and the marriage of cognitive and procedural skills to provide timely lifesaving care to patients is the impetus to enter pulmonary/critical care. Will there be the same attraction to clinical practice in the ICU if our specialty does not maintain its procedural repertoire?

Dr. Pastis is Assistant Professor of Medicine, Department of Medicine, Division of Pulmonary and Critical Care Medicine; Dr. Silvestri is George C. and Margeret Hillenbrand Endowed Professor, Vice-Chair of Faculty Development. Division of Pulmonary and Critical Care Medicine; Medical University of South Carolina, Charleston, South Carolina.

Ideas, but no easy way to ease intensivist shortage

BY SHERRY BOSCHERT
Frontline Medical News

The shortage of intensivists in the critical care game isn't shrinking. What's the best strategy to cope with the shortfall?

Alter the playing field and encourage more players, speakers suggested at a session at the recent Critical Care Congress in San Francisco.

A paper submitted for review by the journal Critical Care Medicine will propose that the Accreditation Council for Graduate Medical Education (ACGME) relax some "very restrictive mandates" on internal medicine–based critical care medicine training programs.

COURTESY MEMORIAL SLOAN-KETTERING CANCER CENTER

Dr. Stephen M. Pastores urged the ACGME to relax mandates on internal medicine–based training programs.

One hurdle requires the critical care medicine program's primary site to offer at least three out of five key fellowship programs. "That can be very difficult for many of the smaller programs that are not major academic centers, where they may not have things like fellowships in infectious diseases, nephrology, pulmonary, et cetera," said Dr. Stephen M. Pastores, FCCP, a lead author of the paper. Dr. Pastores is director of the critical care fellowship program at Memorial Sloan-Kettering Cancer Center, New York, and a board-certified internist, pulmonologist, and intensivist there.

He cochaired a 20-person committee to create proposals for the Critical Care Societies Collaborative's task force on critical care educational pathways in internal medicine.

Another barrier excludes physicians who are not certified in internal medicine from being counted as key faculty in internal medicine–based critical care training programs. "In my program, we have anesthesiologists and surgeons who are teaching our fellows, and there's no good reason they shouldn't be counted as key faculty," Dr. Pastores said at the congress, sponsored by the Society for Critical Care Medicine.

He and Dr. Brian Wessman, who also spoke at the meeting, cited another ACGME barrier, this one blocking the pipeline of emergency medicine physicians. Internal medicine–based critical care medicine training programs must limit the proportion of emergency medicine trainees to 25% of their programs.

However, because their training already includes exposure to undifferentiated critical care patients and development of a "robust procedural acumen applicable to critical care," emergency medicine physicians are the ideal candidates for critical care medicine, Dr. Wessman, an emergency medicine physician and codirector of the critical care fellowship program at Washington University, St. Louis, said at the meeting.

The hospitalist option

Hospitalists are another logical option, particularly because often they are already performing critical care duties. "Even if not hired primarily for that, they're doing it anyway," said Dr. Andrew D. Auerbach, a hospitalist and researcher at the University of California, San Francisco. A 2010 study found that 34 of 72 open intensive care units in Michigan had hospitalists as ICU attending physicians (J. Hosp. Med. 2010;5:4-9). These included smaller hospitals outside major population centers, not just small community hospitals, he said at the meeting.

Intensivists could benefit by forging clinical partnerships with hospitalists to tap hospitalists' expertise in sepsis care, patient monitoring, antimicrobial stewardship, comanaging surgical patients, and transitioning patient care, he suggested.

"Hospitalists want to go into critical care medicine but have been at times in limbo because there is no pathway for them except to do the 2 years of fellowship training," Dr. Pastores agreed in a separate presentation. "We need to help our hospitalists get to the promised land of the ICU," either by creating a shortened training pathway or by offering new incentives.

Community hospitals that want more intensivists could pay for hospitalists to pursue fellowship training and guarantee intensivist jobs when training is finished, said Dr. Pastores.

Hospitals that are determined to have intensivists run the ICU might consider that approach, which could offset the hassle of leaving one's job and taking a temporary pay cut in order to pursue a critical care fellowship, Dr. Franklin A. Michota agreed in an interview. Or, they simply could offer higher salaries to recruit intensivists. "It's a supply-and-demand phenomenon," said Dr. Michota, director of academic affairs in the department of hospitalist medicine at the Cleveland Clinic.

Two years ago, the Society of Hospital Medicine and Society of Critical Care Medicine (SCCM) proposed a 1-year expedited training pathway for "experienced" hospitalists to achieve CCM certification through the ABIM, Dr. Pastores and associates noted in a recent viewpoint article (Crit. Care Med. 2013;41:2754-61).

The proposal was met with deep skepticism by many in the chest physician community. Today, the concept is held by SCCM as a stepping stone toward a much-needed solution to a well-acknowledged problem.

In an interview, SCCM president Dr. Chris Farmer spoke to the issue broadly and with care: "There are not enough intensivists to fill the gap. Many hospitalists currently work in this capacity, and we need to work for longer-term solutions."

The American College of Chest Physicians (CHEST) and the American Association of Critical-Care Nurses have advocated for a "comprehensive approach to improving critical care delivery in the United States" (Chest 2012;142:5), pointing to telemedicine and interdisciplinary strategies to cope with the intensivist shortage rather than endorsing the expedited hospitalist training model.

Internal medicine as pipeline

Besides hospitalists, Dr. Pastores sees greater possibilities from expanding the pipeline of internists into critical care.

"The internal medicine–based trained intensivists really have no competing responsibilities" compared with pulmonologists, surgeons, or other specialists and thus are more likely to work full-time in an ICU, he said. "From that perspective, why are there only 34 stand-alone programs in internal medicine critical care compared to 134 programs in pulmonary critical care? Maybe that could be addressed in a more efficient way."

Pulmonary critical care medicine programs also could be doing more. Dr. Pastores said that although it's not well known, the ACGME allows pulmonary critical care programs every other year to train a fellow who does not want to be certified in pulmonary medicine but wants only to do critical care medicine. If the programs took advantage of that, the number of full-time critical care providers would increase, he said.

The speakers had no relevant disclosures.

Lori Buckner Farmer contributed to this article.

VIEW ON THE NEWS

Dr. Eleanor Summerhill, FCCP, comments: How to address the growing shortfall in board-certified intensivists remains an area of continued debate. Currently, institutions are utilizing telemedicine, physician extenders, and in many instances, hospitalist physicians to fill this gap. At the Society of Critical Care Medicine (SCCM) Critical Care Congress in January 2014, speakers advocated for a number of possible solutions to this problem, largely involving expanding opportunities for further critical care training. These included relaxation of the ACGME mandate requiring that a critical care medicine fellowship's primary training site offer at least three of five key fellowship programs.

Given that there is a significant body of evidence that shows that patients cared for in high-intensity vs. low-intensity intensivist staffing models have reduced mortality and length of stay, going forward it will be important to consider some of these "thinking out of the box" models, while ensuring that alternative training strategies maintain appropriate levels of competency.

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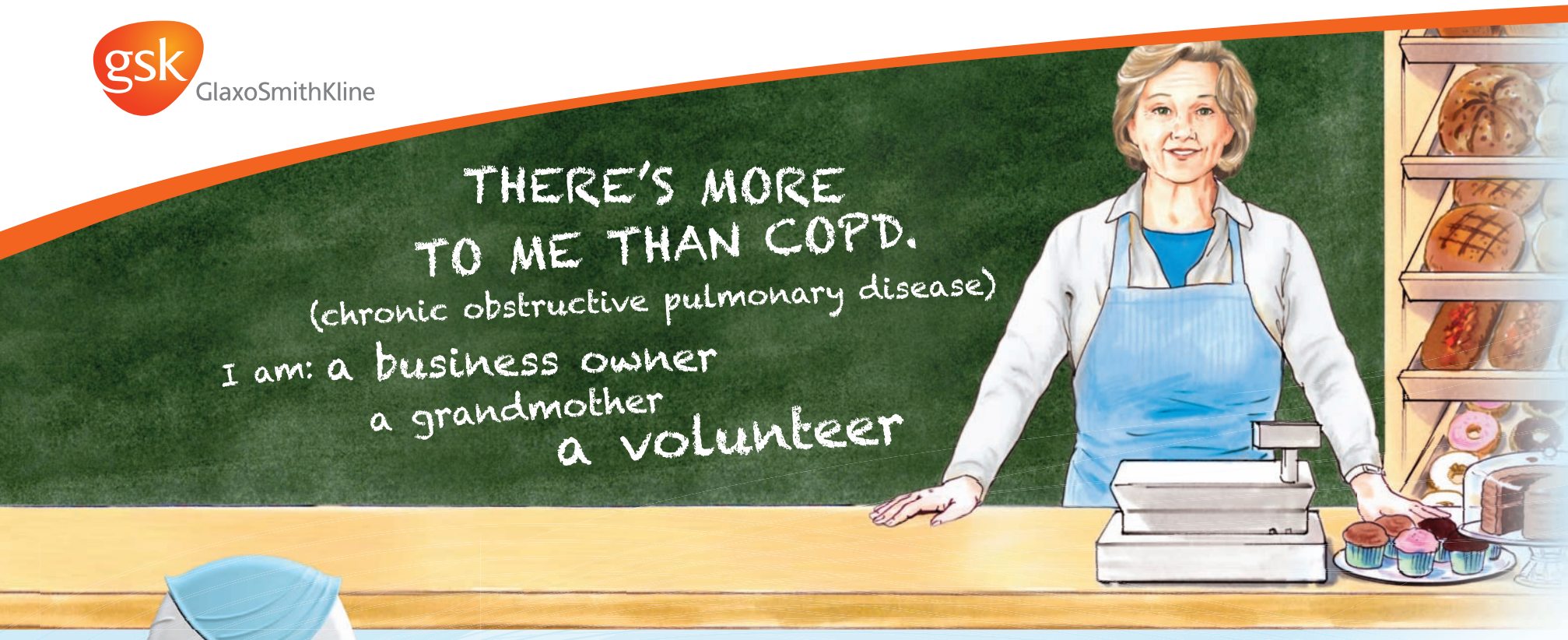

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The only once-daily ICS/LABA (inhaled corticosteroid/long-acting beta$_2$-agonist) for the maintenance treatment of COPD.

Indications

- BREO ELLIPTA is a combination inhaled corticosteroid/long-acting beta$_2$-adrenergic agonist (ICS/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. BREO ELLIPTA is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations.
- BREO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

Important Safety Information for BREO ELLIPTA

WARNING: ASTHMA-RELATED DEATH

- **Long-acting beta$_2$-adrenergic agonists (LABAs), such as vilanterol, one of the active ingredients in BREO 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 LABAs, including vilanterol.**
- **The safety and efficacy of BREO ELLIPTA in patients with asthma have not been established. BREO ELLIPTA is not indicated for the treatment of asthma.**

CONTRAINDICATIONS

- BREO ELLIPTA is contraindicated in patients with severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to either fluticasone furoate, vilanterol, or any of the excipients.

WARNINGS AND PRECAUTIONS

- BREO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.
- BREO ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist.
- BREO ELLIPTA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing LABAs, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using BREO ELLIPTA should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
- Oropharyngeal candidiasis has occurred in patients treated with BREO ELLIPTA. Advise patients to rinse the mouth without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.
- An increase in the incidence of pneumonia has been observed in subjects with COPD receiving BREO ELLIPTA. There was also an increased incidence of pneumonias resulting in hospitalization. In some incidences these pneumonia events were fatal.
  - In replicate 12-month studies of 3255 subjects with COPD who had experienced a COPD exacerbation in the previous year, there was a higher incidence of pneumonia reported in subjects receiving BREO ELLIPTA 100/25 mcg (6% [51 of 806 subjects]), fluticasone furoate (FF)/vilanterol (VI) 50/25 mcg (6% [48 of 820 subjects]), and FF/VI 200/25 mcg (7% [55 of 811 subjects]) than in subjects receiving VI 25 mcg (3% [27 of 818 subjects]). There was no fatal pneumonia in subjects receiving VI or FF/VI 50/25 mcg. There was fatal pneumonia in 1 subject receiving BREO ELLIPTA at the approved strength (100/25 mcg) and in 7 subjects receiving FF/VI 200/25 mcg (<1% for each treatment group).
- Physicians should remain vigilant for the possible development of pneumonia in patients with COPD, as the clinical features of such infections overlap with the symptoms of COPD exacerbations.
- Patients who use corticosteroids are at risk for potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. A more serious or even fatal course of chickenpox or measles may occur in susceptible patients. Use caution in patients with the above because of the potential for worsening of these infections.

BREO ELLIPTA. One inhalation. Once daily.

THE ONLY ONCE-DAILY ICS/LABA FOR THE MAINTENANCE TREATMENT OF COPD

- Approved for long-term, once-daily, maintenance treatment of airflow obstruction in patients with COPD
- Approved to reduce COPD exacerbations in patients with a history of exacerbations
- Not approved for the relief of acute bronchospasm or for the treatment of asthma
- Delivered in the ELLIPTA inhaler

Important Safety Information for BREO ELLIPTA (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. Taper patients slowly from systemic corticosteroids if transferring to BREO ELLIPTA.
- Hypercorticism and adrenal suppression may occur with very high dosages or at the regular dosage of inhaled corticosteroids in susceptible individuals. If such changes occur, discontinue BREO ELLIPTA slowly.
- Caution should be exercised when considering the coadministration of BREO ELLIPTA with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue BREO 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, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, BREO ELLIPTA may need to be discontinued. BREO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
- Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating BREO ELLIPTA and periodically thereafter.
- Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD following the long-term administration of inhaled corticosteroids. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Be alert to hypokalemia and hyperglycemia.

ADVERSE REACTIONS

- The most common adverse reactions (≥3% and more common than placebo) reported in two 6-month clinical trials with BREO ELLIPTA (and placebo) were nasopharyngitis, 9% (8%); upper respiratory tract infection, 7% (3%); headache, 7% (5%); and oral candidiasis, 5% (2%).
- In addition to the events reported in the 6-month studies, adverse reactions occurring in ≥3% of the subjects treated with BREO ELLIPTA in two 1-year studies included COPD, back pain, pneumonia, bronchitis, sinusitis, cough, oropharyngeal pain, arthralgia, hypertension, influenza, pharyngitis, diarrhea, peripheral edema, and pyrexia.

DRUG INTERACTIONS

- Caution should be exercised when considering the coadministration of BREO ELLIPTA with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and cardiovascular adverse effects may occur.
- BREO 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 reversible obstructive airways disease.
- Use with caution in patients taking non–potassium-sparing diuretics, as electrocardiographic changes and/or hypokalemia associated with non–potassium-sparing diuretics may worsen with concomitant beta-agonists.

USE IN SPECIFIC POPULATIONS

- Use BREO ELLIPTA with caution in patients with moderate or severe hepatic impairment. Fluticasone furoate exposure may increase in these patients. Monitor for systemic corticosteroid effects.

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

BREO ELLIPTA was developed in collaboration with Theravance

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

BREO™ ELLIPTA™
(fluticasone furoate 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 LABA, including vilanterol, an active ingredient in BREO ELLIPTA *[see Warnings and Precautions (5.1)]*.

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

1 INDICATIONS AND USAGE

BREO ELLIPTA is a combination inhaled corticosteroid/long-acting beta$_2$-adrenergic agonist (ICS/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. BREO ELLIPTA is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations.

Important Limitations of Use: BREO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

4 CONTRAINDICATIONS

The use of BREO ELLIPTA is contraindicated in patients with severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to either fluticasone furoate, vilanterol, or any of the excipients *[see Warnings and Precautions (5.11), Description (11) of full prescribing information]*.

5 WARNINGS AND PRECAUTIONS

5.1 Asthma-Related Death 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 BREO ELLIPTA. No study adequate to determine whether the rate of asthma-related death is increased in subjects treated with BREO ELLIPTA has been conducted. The safety and efficacy of BREO ELLIPTA in patients with asthma have not been established. BREO ELLIPTA is not indicated for the treatment of asthma.

5.2 Deterioration of Disease and Acute Episodes BREO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD. BREO ELLIPTA has not been studied in patients with acutely deteriorating COPD. The initiation of BREO ELLIPTA in this setting is not appropriate. BREO ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. BREO 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 BREO 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 BREO 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 BREO 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 BREO ELLIPTA beyond the recommended dose is not appropriate in this situation.

5.3 Excessive Use of BREO ELLIPTA and Use With Other Long-Acting Beta$_2$-Agonists BREO 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 BREO ELLIPTA should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

5.4 Local Effects of Inhaled Corticosteroids In clinical trials, the development of localized infections of the mouth and pharynx with *Candida albicans* has occurred in subjects treated with BREO ELLIPTA. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while treatment with BREO ELLIPTA continues, but at times therapy with BREO ELLIPTA may need to be interrupted. Advise the patient to rinse his/her mouth without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.

5.5 Pneumonia An increase in the incidence of pneumonia has been observed in subjects with COPD receiving the fluticasone furoate/vilanterol combination, including BREO ELLIPTA 100 mcg/25 mcg, in clinical trials. There was also an increased incidence of pneumonias resulting in hospitalization. In some incidences these pneumonia events were fatal. Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations. In replicate 12-month trials in 3,255 subjects with COPD who had experienced a COPD exacerbation in the previous year, there was a higher incidence of pneumonia reported in subjects receiving the fluticasone furoate/vilanterol combination (50 mcg/25 mcg: 6% [48 of 820 subjects]; 100 mcg/25 mcg: 6% [51 of 806 subjects]; or 200 mcg/25 mcg: 7% [55 of 811 subjects]) than in subjects receiving vilanterol 25 mcg (3% [27 of 818 subjects]). There was no fatal pneumonia in subjects receiving vilanterol or fluticasone furoate/vilanterol 50 mcg/25 mcg. There was fatal pneumonia in 1 subject receiving fluticasone furoate/vilanterol 100 mcg/25 mcg and in 7 subjects receiving fluticasone furoate/vilanterol 200 mcg/25 mcg (less than 1% for each treatment group).

5.6 Immunosuppression Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If a patient is exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered. Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

5.7 Transferring Patients From Systemic Corticosteroid Therapy Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. Patients who have been previously maintained on 20 mg or more of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although BREO ELLIPTA may control COPD symptoms during these episodes, in recommended doses it supplies less than normal physiological amount of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies. During periods of stress or a severe COPD exacerbation, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or severe COPD exacerbation. Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to BREO ELLIPTA. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with BREO ELLIPTA. Lung function (mean forced expiratory volume in 1 second [FEV_1]), beta-agonist use, and COPD symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension. Transfer of patients from systemic corticosteroid therapy to BREO ELLIPTA may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions). During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, and depression) despite maintenance or even improvement of respiratory function.

5.8 Hypercorticism and Adrenal Suppression Inhaled fluticasone furoate is absorbed into the circulation and can be systemically active. Effects of fluticasone furoate on the HPA axis are not observed with the therapeutic dose of BREO ELLIPTA. However, exceeding the recommended dosage or coadministration with a strong cytochrome P450 3A4 (CYP3A4) inhibitor may result in HPA dysfunction *[see Warnings and Precautions (5.9), Drug Interactions (7.1)]*. Because of the possibility of significant systemic absorption of inhaled corticosteroids in sensitive patients, patients treated with BREO ELLIPTA should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response. It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients who are sensitive to these effects. If such effects occur, BREO ELLIPTA should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids, and other treatments for management of COPD symptoms should be considered.

5.9 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors Caution should be exercised when considering the coadministration of BREO ELLIPTA with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full prescribing information]*.

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

5.11 Hypersensitivity Reactions Hypersensitivity reactions may occur after administration of BREO 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 take BREO ELLIPTA *[see Contraindications (4)]*.

5.12 Cardiovascular Effects Vilanterol, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, BREO 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. In healthy subjects, large doses of inhaled fluticasone furoate/vilanterol (4 times the recommended dose of vilanterol, representing a 12-fold higher systemic exposure than seen in patients with COPD) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias. Therefore, BREO ELLIPTA, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5.13 Reduction in Bone Mineral Density Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating BREO ELLIPTA and periodically thereafter. If significant reductions in BMD are seen and BREO ELLIPTA is still considered medically important for that patient's COPD therapy, use of medicine to treat or prevent osteoporosis should be strongly considered. In replicate 12-month trials in 3,255 subjects with COPD, bone fractures were reported by 2% of subjects receiving the fluticasone furoate/vilanterol combination (50 mcg/25 mcg: 2% [14 of 820 subjects]; 100 mcg/25 mcg: 2% [19 of 806 subjects]; or 200 mcg/25 mcg: 2% [14 of 811 subjects]) than in subjects receiving vilanterol 25 mcg alone (less than 1% [8 of 818 subjects]).

5.14 Glaucoma and Cataracts Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD following the long-term administration of inhaled corticosteroids. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts. In replicate 12-month trials in 3,255 subjects with COPD, similar incidences of ocular effects (including glaucoma and cataracts) were reported in subjects receiving the fluticasone furoate/vilanterol combination (50 mcg/25 mcg: less than 1% [7 of 820 subjects]; 100 mcg/25 mcg: 1% [12 of 806 subjects]; 200 mcg/25 mcg: less than 1% [7 of 811 subjects]) as those receiving vilanterol 25 mcg alone (1% [9 of 818 subjects]).

5.15 Coexisting Conditions BREO 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.

5.16 Hypokalemia and Hyperglycemia Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medications may produce transient hyperglycemia in some patients. In 4 clinical trials of 6- and 12-month duration evaluating BREO 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 BREO ELLIPTA, increase the risk of asthma-related death. BREO ELLIPTA is not indicated for the treatment of asthma. *[See Boxed Warnings and Warnings and Precautions (5.1).]* Systemic and local corticosteroid use may result in the following: Increased risk of pneumonia in COPD *[see Warnings and Precautions (5.5)]*; Increased risk for decrease in bone mineral density *[see Warnings and Precautions (5.13)]*.

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 BREO ELLIPTA included 7,700 subjects with COPD in two 6-month lung function trials, two 12-month exacerbation trials, and 6 other trials of shorter duration. A total of 2,034 subjects have received at least 1 dose of BREO ELLIPTA 100 mcg/25 mcg, and 1,087 subjects have received higher doses of fluticasone furoate/vilanterol. The safety data described below are based on the confirmatory 6-month and 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 BREO ELLIPTA in Table 1 is based on 2 placebo-controlled, 6-month clinical trials (Trials 1 and 2; n = 1,224 and n = 1,030, respectively). Of the 2,254 subjects, 70% were male and 84% were Caucasian. They had a mean age of 62 years and an average smoking history of 44 pack

years, with 54% identified as current smokers. At screening, the mean postbronchodilator percent predicted FEV_1 was 48% (range: 14% to 87%), the mean postbronchodilator FEV_1/forced vital capacity (FVC) ratio was 47% (range: 17% to 88%), and the mean percent reversibility was 14% (range: -41% to 152%). Subjects received 1 inhalation once daily of the following: BREO ELLIPTA 100 mcg/25 mcg, fluticasone furoate/vilanterol 50 mcg/25 mcg, fluticasone furoate/vilanterol 200 mcg/25 mcg, fluticasone furoate 100 mcg, fluticasone furoate 200 mcg, vilanterol 25 mcg, or placebo.

Table 1. Adverse Reactions With ≥3% Incidence and More Common Than Placebo With BREO ELLIPTA in Subjects With Chronic Obstructive Pulmonary Disease

Adverse Event	BREO ELLIPTA 100 mcg/25 mcg (n = 410) %	Vilanterol 25 mcg (n = 408) %	Fluticasone Furoate 100 mcg (n = 410) %	Placebo (n = 412) %
Infections and infestations				
Nasopharyngitis	9	10	8	8
Upper respiratory tract infection	7	5	4	3
Oropharyngeal candidiasis[a]	5	2	3	2
Nervous system disorders				
Headache	7	9	7	5

[a]Includes terms oral candidiasis, oropharyngeal candidiasis, candidiasis, and oropharyngitis fungal.

12-Month Trials: Long-term safety data is based on two 12-month trials (Trials 3 and 4; n = 1,633 and n = 1,622, respectively). Trials 3 and 4 included 3,255 subjects, of which 57% were male and 85% were Caucasian. They had a mean age of 64 years and an average smoking history of 46 pack years, with 44% identified as current smokers. At screening, the mean postbronchodilator percent predicted FEV_1 was 45% (range: 12% to 91%), and the mean postbronchodilator FEV_1/FVC ratio was 46% (range: 17% to 81%), indicating that the subject population had moderate to very severely impaired airflow obstruction. Subjects received 1 inhalation once daily of the following: BREO ELLIPTA 100 mcg/25 mcg, fluticasone furoate/vilanterol 50 mcg/25 mcg, fluticasone furoate/vilanterol 200 mcg/25 mcg, or vilanterol 25 mcg. In addition to the events shown in Table 1, adverse reactions occurring in greater than or equal to 3% of the subjects treated with BREO ELLIPTA (N = 806) for 12 months included COPD, back pain, pneumonia *[see Warnings and Precautions (5.5)]*, bronchitis, sinusitis, cough, oropharyngeal pain, arthralgia, hypertension, influenza, pharyngitis, diarrhea, peripheral edema, and pyrexia.

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4 Fluticasone furoate and vilanterol, the individual components of BREO ELLIPTA, are both substrates of CYP3A4. Concomitant administration of the potent CYP3A4 inhibitor ketoconazole increases the systemic exposure to fluticasone furoate and vilanterol. Caution should be exercised when considering the coadministration of BREO ELLIPTA with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) *[see Warnings and Precautions (5.9) and Clinical Pharmacology (12.3) of full prescribing information]*.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants Vilanterol, like other $beta_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

7.3 Beta Adrenergic Receptor Blocking Agents Beta-blockers not only block the pulmonary effect of beta-agonists, such as vilanterol, a component of BREO ELLIPTA, but may produce severe bronchospasm in patients with reversible obstructive airways disease. 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, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with non–potassium-sparing diuretics.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled trials with BREO ELLIPTA in pregnant women. Corticosteroids and $beta_2$-agonists have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Because animal studies are not always predictive of human response, BREO 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 BREO ELLIPTA. *Fluticasone Furoate and Vilanterol:* There was no evidence of teratogenic interactions between fluticasone furoate and vilanterol in rats at approximately 9 and 40 times, respectively, the maximum recommended human daily inhalation dose (MRHDID) in adults (on a mcg/m^2 basis at maternal inhaled doses of fluticasone furoate and vilanterol, alone or in combination, up to approximately 95 mcg/kg/day). *Fluticasone Furoate:* There were no teratogenic effects in rats and rabbits at approximately 9 and 2 times, respectively, the MRHDID in adults (on a mcg/m^2 basis at maternal inhaled doses up to 91 and 8 mcg/kg/day in rats and rabbits, respectively). There were no effects on perinatal and postnatal development in rats at approximately 3 times the MRHDID in adults (on a mcg/m^2 basis at maternal doses up to 27 mcg/kg/day). *Vilanterol:* There were no teratogenic effects in rats and rabbits at approximately 13,000 and 160 times, respectively, the MRHDID in adults (on a mcg/m^2 basis at maternal inhaled doses up to 33,700 mcg/kg/day in rats and on an AUC basis at maternal inhaled doses up to 591 mcg/kg/day in rabbits). However, fetal skeletal variations were observed in rabbits at approximately 1,000 times the MRHDID in adults (on an AUC basis at maternal inhaled or subcutaneous doses of 5,740 or 300 mcg/kg/day, respectively). The skeletal variations included decreased or absent ossification in cervical vertebral centrum and metacarpals. There were no effects on perinatal and postnatal development in rats at approximately 3,900 times the MRHDID in adults (on a mcg/m^2 basis at maternal oral doses up to 10,000 mcg/kg/day).
Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully monitored.

8.2 Labor and Delivery There are no adequate and well-controlled human trials that have investigated the effects of BREO ELLIPTA during labor and delivery. Because beta-agonists may potentially interfere with uterine contractility, BREO ELLIPTA should be used during labor only if the potential benefit justifies the potential risk.

8.3 Nursing Mothers It is not known whether fluticasone furoate or vilanterol are excreted in human breast milk. However, other corticosteroids and $beta_2$-agonists have been detected in human milk. Since there are no data from controlled trials on the use of BREO ELLIPTA by nursing mothers, caution should be exercised when it is administered to a nursing woman.

8.5 Geriatric Use Based on available data, no adjustment of the dosage of BREO ELLIPTA in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out. Clinical trials of BREO ELLIPTA for COPD included 2,508 subjects aged 65 and older and 564 subjects 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 Fluticasone furoate systemic exposure increased by up to 3-fold in subjects with hepatic impairment compared with healthy subjects. Hepatic impairment had no effect on vilanterol systemic exposure. Use BREO ELLIPTA with caution in patients with moderate or severe hepatic impairment. Monitor patients for corticosteroid-related side effects *[see Clinical Pharmacology (12.3) of full prescribing information]*.

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

10 OVERDOSAGE

No human overdosage data has been reported for BREO ELLIPTA. BREO ELLIPTA contains both fluticasone furoate and vilanterol; therefore, the risks associated with overdosage for the individual components described below apply to BREO ELLIPTA.

10.1 Fluticasone Furoate Because of low systemic bioavailability (15.2%) and an absence of acute drug-related systemic findings in clinical trials, overdosage of fluticasone furoate is unlikely to require any treatment other than observation. If used at excessive doses for prolonged periods, systemic effects such as hypercorticism may occur *[see Warnings and Precautions (5.8)]*. Single- and repeat-dose trials of fluticasone furoate at doses of 50 to 4,000 mcg have been studied in human subjects. Decreases in mean serum cortisol were observed at dosages of 500 mcg or higher given once daily for 14 days.

10.2 Vilanterol The expected signs and symptoms with overdosage of vilanterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms of beta-adrenergic stimulation (e.g., 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. Treatment of overdosage consists of discontinuation of BREO 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

BREO ELLIPTA: No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with BREO ELLIPTA; however, studies are available for the individual components, fluticasone furoate and vilanterol, as described below.
Fluticasone Furoate: Fluticasone furoate produced no treatment-related increases in the incidence of tumors in 2-year inhalation studies in rats and mice at inhaled doses up to 9 and 19 mcg/kg/day, respectively (approximately equal to the MRHDID in adults on a mcg/m^2 basis). Fluticasone furoate did not induce gene mutation in bacteria or chromosomal damage in a mammalian cell mutation test in mouse lymphoma L5178Y cells in vitro. There was also no evidence of genotoxicity in the in vivo micronucleus test in rats. No evidence of impairment of fertility was observed in male and female rats at inhaled fluticasone furoate doses up to 29 and 91 mcg/kg/day, respectively (approximately 3 and 9 times, respectively, the MRHDID in adults on a mcg/m^2 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 8,750 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 530 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 45 times the MRHDID in adults on an AUC basis). No tumors were seen at an inhalation dose of 10.5 mcg/kg/day (approximately 2 times 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 14,000 times, respectively, the MRHDID in adults on a mcg/m^2 basis).

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide and Instructions for Use)

17.1 Asthma-Related Death Patients should be informed that LABA, such as vilanterol, one of the active ingredients in BREO ELLIPTA, increase the risk of asthma-related death. BREO ELLIPTA is not indicated for the treatment of asthma.

17.2 Not for Acute Symptoms BREO ELLIPTA is not meant to relieve acute symptoms of COPD and extra doses should not be used for that purpose. Acute symptoms should be treated with a rescue inhaler such as albuterol. The physician should provide the patient with such medicine and instruct the patient in how it should be used. Patients should be instructed to notify their physicians immediately if they experience any of the following: Symptoms get worse; Need for more inhalations than usual of their rescue inhaler; Significant decrease in lung function as outlined by the physician. Patients should not stop therapy with BREO ELLIPTA without physician/provider guidance since symptoms may recur after discontinuation.

17.3 Do Not Use Additional Long-Acting $Beta_2$-Agonists When patients are prescribed BREO ELLIPTA, other medicines containing a LABA should not be used.

17.4 Risks Associated With Corticosteroid Therapy

Local Effects: Patients should be advised that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing therapy with BREO ELLIPTA, but at times therapy with BREO ELLIPTA may need to be temporarily interrupted under close medical supervision. Rinsing the mouth without swallowing after inhalation is advised to help reduce the risk of thrush.
Pneumonia: Patients with COPD who have received BREO ELLIPTA have a higher risk of pneumonia and should be instructed to contact their healthcare providers if they develop symptoms of pneumonia (e.g., fever, chills, change in sputum color, increase in breathing problems).
Immunosuppression: Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to consult their physicians without delay. Patients should be informed of potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infections, or ocular herpes simplex.
Hypercorticism and Adrenal Suppression: Patients should be advised that BREO ELLIPTA may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, patients should be instructed that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids.
Reduction in Bone Mineral Density: Patients who are at an increased risk for decreased BMD should be advised that the use of corticosteroids may pose an additional risk.
Ocular Effects: Long-term use of inhaled corticosteroids may increase the risk of some eye problems (cataracts or glaucoma); regular eye examinations should be considered.

17.5 Risks Associated With Beta-Agonist Therapy Patients should be informed of adverse effects associated with $beta_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

GlaxoSmithKline
Research Triangle Park, NC 27709

Revised 05/2013 BRE:1BRS

Varenicline plus CBT keeps tobacco at bay

BY MARY ANN MOON
Frontline Medical News

Patients with serious mental illness who quit smoking with a standard 12-week course of varenicline and cognitive-behavioral therapy are three times more likely to maintain that abstinence if they take a maintenance dose of the drug than if they discontinue it, a study has shown.

In what the researchers described as the first randomized controlled clinical trial of maintenance pharmacotherapy aimed at preventing smoking relapse in people with serious mental illness, the prevalence of smoking abstinence after 1 year was 60% (24 of 40 study participants) in patients assigned to maintenance varenicline, compared with 19% (9 of 47 participants) in those assigned to placebo.

"Such maintenance treatment may reduce the high prevalence of tobacco dependence and reduce the heavy burden of smoking-related morbidity and mortality in those with serious mental illness," Dr. A. Eden Evins of Massachusetts General Hospital and Harvard Medical School, Boston, and her associates wrote in JAMA.

The open-label study, released in advance of the 50th anniversary of the Surgeon General's Report on Smoking and Health, involved 203 adults with schizophrenia spectrum disorder (185 patients) or bipolar disorder (18 patients) who reported smoking 10 or more cigarettes per day and whose expired carbon monoxide levels were higher than 9 ppm at baseline. All were outpatients at 10 community health centers in Massachusetts, Michigan, New Hampshire, Indiana, Alabama, or Minnesota, and all were taking stable doses of antipsychotic or mood- stabilizing medication.

A total of 87 of these participants successfully completed a 12-week smoking cessation program combining up to 1.0 mg of varenicline twice daily plus weekly 1-hour group cognitive-behavioral therapy (CBT) sessions. They were randomly assigned to continue for another 40 weeks with either CBT plus 1.0 mg of varenicline twice daily (40 patients) or CBT plus matching placebo (47 patients).

The CBT, which focused on relapse-prevention skills, was tapered from weekly to monthly sessions, for a total of 15 sessions during the 40 weeks.

At 52 weeks from baseline, smoking cessation treatment was stopped, and the 59 patients remaining in the study were followed through week 64 for biochemically verified smoking abstinence and safety outcomes.

At week 52, 24 of 40 participants taking maintenance varenicline (60%) were still abstaining from smoking, compared with only 9 of the 47 patients (19%) taking placebo, for an odds ratio of 6.2. At week 64, 18 participants (45%) in the varenicline group were still abstaining from smoking, compared with only 6 (13%) in the placebo group, for an odds ratio of 5.1, Dr. Evins and her associates reported (JAMA 2014 Jan. 7 [doi: 10.1001/jama.2013.285113]).

During treatment and follow-up, the two study groups showed no differences in the severity of their psychiatric symptoms, nicotine withdrawal symptoms, or self-reported overall health. No serious adverse events were attributed to the study medication.

However, because of the small sample size and the high dropout rate of the study, "it is not possible to accurately estimate the risk of serious adverse effects or to make claims regarding safety," investigators noted.

This study was funded by the National Institute on Drug Abuse and Pfizer. Pfizer also supplied the study medication and provided other support. Dr. Evins and her associates reported ties to Pfizer.

VIEW ON THE NEWS

Dr. Vera DePalo, FCCP, comments: Tobacco use is a risk factor for the development of several pathologies. Cessation is particularly difficult in patients with serious mental illness. This study holds promise for success in smoking cessation. While no serious adverse events were attributed to the medication, the authors point out, with the small sample size and the study drop out rate, more investigation is needed to accurately make claims about safety.

Surgeon general report links smoking to many diseases

BY ALICIA AULT
Frontline Medical News

While smoking rates have dropped precipitously since the landmark 1964 surgeon general's report, "Smoking and Health," smoking is still the leading cause of preventable disease and death in the United States and is now causally linked to additional diseases and conditions across most organ systems.

A new surgeon general's report, "The Health Consequences of Smoking – 50 Years of Progress," released at a White House event last month, synthesizes original and review evidence in an effort to further federal antismoking efforts.

The report causally links cigarette smoking to type 2 diabetes, rheumatoid arthritis, ectopic pregnancy, and erectile dysfunction. Secondhand smoke is now causally linked to cancers, respiratory diseases, and cardiovascular diseases, as well as adverse effects on the health of children, the authors wrote.

In addition, the 980-page report establishes that secondhand smoke is a cause of stroke, and that smoking increases the risk of dying in cancer patients and cancer survivors.

Another finding: Cigarette smokers today have a higher risk of lung cancer than did those who smoked in 1964, because of the higher number of chemical additives now used.

Women smokers now have the same risk of death from lung cancer as that of men and a higher relative risk of dying from coronary heart disease than that of men. Because of smoking, the number of women dying from chronic obstructive pulmonary disease (COPD) is now higher than in men.

With this report, the federal government launches a new effort to prevent children from using tobacco.

"Today, we're asking Americans to join a sustained effort to make the next generation a tobacco-free generation," Health & Human Services Secretary Kathleen Sebelius said in a statement. "This is not something the federal government can do alone. We need to partner with the business community, local elected officials, schools and universities, the medical community, the faith community, and committed citizens in communities across the country to make the next generation tobacco free."

The report finds that youth smoking rates declined by 50% between 1997 and 2011, but 3,200 children under age 18 still start smoking each day, and an additional 2,100 youth and young adults become daily smokers. The report places most of the blame for continued interest in smoking on the tobacco industry, saying it has used "aggressive strategies" to deliberately mislead the public about the harms of smoking.

Acting Surgeon General Boris Lushniak noted that smoking rates are disproportionately higher among people with less education and lower incomes, among the mentally ill, and among gay, lesbian, bisexual, and transgender individuals.

Dr. Lushniak and other officials at the White House event called for greater tobacco control efforts, including stricter regulation. The Food and Drug Administration was given the power to regulate tobacco through the 2009 Family Smoking Prevention and Tobacco Control Act.

Dr. Lushniak noted that for current and about-to-start smokers, "the clock is ticking – they can't wait for slow and steady progress to end the epidemic. Enough is enough."

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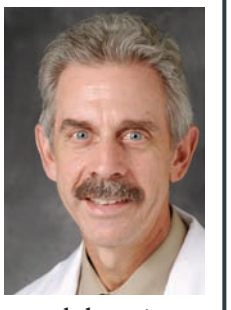
VIEW ON THE NEWS



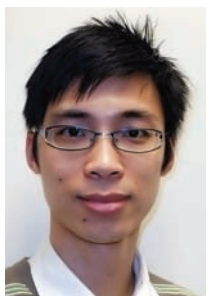
Dr. Daniel Ouellette, FCCP, comments: Americans received a wake-up call in 1964 when the Surgeon General announced that smoking cigarettes was dangerous to one's health. The current report links cigarette smoking and secondhand smoke exposure to a number of nonrespiratory diseases. Findings also include the fact that cigarettes today are more toxic than those of 50 years ago. The rates of many smoking-related diseases in women now equal those in men, and children continue to start smoking at alarming rates. What should physicians do? Counsel all of your patients to quit smoking!

Perception of safety may spur e-cigarette use

BY M. ALEXANDER OTTO
Frontline Medical News

Debunking popular notions about electronic cigarettes – that they're safer than real ones and help people quit smoking – might deter young adults from trying them, according to a recent study published ini the American Journal of Preventive Medicine.

The investigators asked 1,379 20-somethings who had never tried e-cigarettes what they thought about the products, and then resurveyed the group a year later to see who had tried them.



Almost 12% of people who had quit smoking at baseline were reintroduced to nicotine through e-cigarettes.

DR. CHOI

More than 10% of those who thought e-cigarettes were less harmful than tobacco ones, but only 4.6% of those who did not, had tried e-cigarettes within a year (odds ratio, 2.34; 95% confidence interval, 1.49-3.69).

Similarly, 10% who thought that e-cigarettes could help people quit smoking, but only 5.4% who did not, had tried them (OR, 1.98; 95% CI, 1.29-3.04). The results were adjusted for age, sex, education, and baseline smoking status (Am. J. Prev. Med. 2014;46:175-8).

The findings "suggest that messages about the lack of evidence on e-cigarettes being cessation aids, and the uncertainty of the risks associated with e-cigarette use" – addiction, pneumonia, heart failure, and so on – "may discourage young adults from experimenting with e-cigarettes," said investigators Kelvin Choi, Ph.D., of the National Institute on Minority Health and Health Disparities in Bethesda, Md., and Jean Forster, Ph.D., of the University of Minnesota, Minneapolis.

"Although a recent review of the literature on e-cigarettes suggests that [they] may be a viable reduced-harm alternative to cigarettes, previous studies have found that experimentation with e-cigarettes was not associated with intention to quit, making quit attempts, or smoking cessation," they said.

At the 1-year follow-up, 7.4% (102) of the sample reported trying e-cigarettes, including 2.9% (28) of baseline nonsmokers. Almost 22% (53) of smokers and 11.9% (21) of former smokers had, as well, meaning that almost 12% of people who said they had quit smoking at baseline were reintroduced to nicotine through e-cigarettes, the authors noted.

The participants were members of the Minnesota Adolescent Community Cohort. The study sample was split about evenly between men and women, and most of the subjects were white, which could limit the findings' generalizability, the authors said.

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Imaging techniques target bronchial thermoplasty

BY PATRICE WENDLING
Frontline Medical News

CHICAGO – Advanced imaging techniques may play an increasing role in targeting the delivery of bronchial thermoplasty in severe, uncontrolled asthma.

"It's off-label at this point, but I think this is where we're going with this therapy," Dr. Mario Castro, FCCP, said at the annual meeting of the American College of Chest Physicians. "Perhaps we can do a better job to target this therapy, just like phenotyping our patients [for novel biologic agents]."

Reconstruction of the airway and parenchyma using diagnostic software during an inspiratory computed tomography (CT) scan allows clinicians to measure all of the lung airways in a systematic way, said Dr. Castro, director of the asthma and airway translational research unit, Washington University School of Medicine, St. Louis.

In the case of a 50-year-old patient with severe persistent asthma, the technique revealed a clearly remodeled airway with a 63% average wall area, but also areas of great heterogeneity in all segmental airways. "What we find is that some airways are remodeled more than others," Dr. Castro said.

Reconstruction of the airway and parenchyma using diagnostic software during an inspiratory CT scan allows clinicians to measure all of the lung airways in a systematic way.

The university also now images its patients by combining inhaled hyperpolarized helium gas with magnetic resonance imaging from the apex all the way to the base of the lung. A color algorithm CT mask imposed on the MRI allows the team to quantify ventilation defects before and after bronchial thermoplasty.

Earlier this year, Dr. Castro's colleague, Dr. Ajay Sheshadri, reported that patients with severe asthma have a higher baseline ventilation defect percentage (VDP) than healthy subjects (mean 24.4% vs. 3.5%; $P = .003$). VDP improved by about 7% overall after bronchial thermoplasty

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($P = .10$), with some patients having a marked improvement in VDP, while others did not, Dr. Castro said.

Baseline characteristics were analyzed in an effort to identify responders, and "we were very surprised to find that sputum eosinophilia was the one that trended best in predicting a change in ventilation defect score," he added.

Dr. Castro's team is also using xenon gas instead of helium with MRI, because it is more readily available and less expensive. Other groups are using confocal CT to evaluate airways for bronchial thermoplasty, he noted.

Dr. Castro stressed that 13 years of cumulative experience have shown that bronchial thermoplasty is safe and effective, but that careful initial evaluation of candidates remains essential. The American Thoracic Society and European Respiratory Society are expected to release new guidelines early next year for the initial evaluation of all severe asthmatics that recommend six tests, including blood work, spirometry, immunoglobulin E assessment with skin prick tests or an immunoabsorbent assay, and multidetector CT, to evaluate for other conditions mimicking asthma.

"With this basic evaluation in our center, we find about one out of every three patients are really not pure asthma; they're asthma mixed with significant bronchiectasis or no asthma at all, or they have underlying emphysema from prior smoke exposure," said Dr. Castro. "So it is very important that we take a step back with these patients and look."

During a discussion following the presentation, Dr. Castro said he would use bronchial thermoplasty to treat patients with incomplete reversibility of airflow obstruction, but does not advocate repeat treatments because of the potential for additional injury.

"What we do advocate is that we extensively treat all the airways that we can access, and that you treat with continuous therapies," he said. "The average activations in the lower, lower [airway] is around 60, but in some cases I've done up to around 140-150 activations, just because they've had an extensive bronchial tree that I needed to treat. … If you have a nonresponder, even 5 years out, I wouldn't treat because I think smooth muscle is probably not their main problem."

Dr. Castro reported research support, lecturing, and consulting for numerous firms including Boston Scientific, maker of the Alair bronchial thermoplasty system.

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VIEW ON THE NEWS

Dr. Eric Gartman, FCCP, comments: Severe asthma patients are a heterogenous population, and any modality that augments our ability to discriminate the best treatment option for an individual patient is eagerly welcomed.

As this field of research matures, we may begin to tailor our therapies more effectively to those who will benefit most.

Comfort care informs critical care's Choosing Wisely list

BY SHERRY BOSCHERT
Frontline Medical News

SAN FRANCISCO – Four critical care societies released a list of the top five things that intensivists should avoid doing, part of the larger Choosing Wisely campaign to reduce unnecessary and costly medical practices. The list, released at the Critical Care Congress, includes a potentially difficult issue: offering patients' families the option of discontinuation of life support in lieu of comfort care.

Fifth on the list, the life-support item may be the most controversial and is also the one that the representatives felt the most strongly about including on the list, whether it saves many resources or not, according to Dr. Hannah Wunsch of Columbia University Medical Center, New York, who served on the collaborative task force. "Many … patients re-

ONLINE EXTRAS

Dr. Edward Conway of Beth Israel Med Center applauded the list. Scan the QR code to watch a video online.

ceive aggressive life-sustaining therapies, in part due to clinicians' failures to elicit patients' values and goals, and to provide patient-centered recommendations," the task force wrote.

The Society for Critical Care Medicine, which sponsored the congress, collaborated with the American College of Chest Physicians, the American Thoracic Society, and the American Association of Critical Care Nurses to create the list.

It includes these top five "don'ts":

1. Don't order diagnostic tests at regular intervals (such as every day), but rather in response to specific clinical questions. Ordering diagnostic studies such as x-rays, arterial blood gases, blood counts, blood chemistries, or ECGs daily or at routine intervals drives up costs, doesn't benefit patients, and may harm them through radiation exposure, inducing anemia, or triggering aggressive follow-up of incidental results.

2. Don't transfuse red blood cells in hemodynamically stable, non-bleeding ICU patients with a hemoglobin concentration greater than 7 mg/dL. Blood is a scarce resource, and studies show that limiting red blood cell transfusions to thresholds of 7 mg/dL or higher does not worsen survival, complications, or costs, and causes fewer complications. Different thresholds may be appropriate for patients with ACS, but even in this subgroup aggressive transfusion is harmful, most observational studies suggest.

3. Don't use parenteral nutrition in adequately nourished critically ill patients within the first 7 days of an ICU stay. Early parenteral nutrition is harmful, even in patients who cannot tolerate enteral nutrition, if they were adequately nourished prior to ICU admission. The evidence is less clear for patients with nosocomial infections, and early parenteral nutrition may benefit patients who were severely malnourished right before ICU admission. A study to be published soon shows that 90% of parenteral nutrition in the United States starts within 7 days of admission, usually within the first 2 days, Dr. Wunsch said.

4. Don't deeply sedate mechanically ventilated patients without a specific indication and without daily attempts to lighten sedation. Deep sedation of patients on MV prolongs the duration of ventilation and hospitalization. Several protocols for limiting sedation have been shown to improve outcomes.

5. Don't continue life support for patients at high risk of death or severely impaired functional recovery without offering patients and their families the alternative of care focused entirely on comfort. When an audience member expressed concern about discontinuation of life support possibly increasing premature deaths, Dr. Wunsch stressed that the second part of the statement is key – giving the family the choice of comfort care or continuing life support.

The CHEST Foundation Giving Club

The CHEST Foundation is pleased to announce the new Annual Fund Recognition and Benefits for donors

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We're Moving: New CHEST Global Headquarters opens in February

The new CHEST Global Headquarters opens this month, allowing us to take the next great leap in advancing the future of chest medicine.

This year, we'll offer more than 15 live learning courses in CHEST's state-of-the-art Innovation, Simulation, and Training Center, a high-tech, interactive facility for delivering clinical education and hands-on training in pulmonary, critical care, and sleep medicine. This one-of-a-kind center—your connection to year-round immersive training and education—features an auditorium, simulation ICU rooms, education breakout rooms, and wet and dry innovation labs, so you and members of your team can come together for collaborative learning that helps you put the latest clinical advances into immediate practice. Learn more at chestnet.org/center.

Our new address and phone number:
CHEST Global Headquarters
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NETWORKS: Pragmatism, therapeutic hypothermia, IIP, and farewell to a home care champion

Clinical Research

What's a clinical scientist to do? A pragmatic approach to study design

With the continued increasing cost of health care in the United States and implementation of the Patient Protection and Affordable Health Care Act (ACA), there is a focus on comparative effectiveness research (CER). The purpose of CER is to provide evidence on the effectiveness, benefits, and harms of different treatment options in real patient populations and practice settings. The resulting data are expected to improve the ability of policy makers, consumers, payers, and providers to make informed decisions about health care.

Randomized clinical trials (RCTs) measure the presence and effect of an intervention by tightly controlling for variables, often creating a homogenous subject group. Although RCTs satisfy regulatory requirements for safety and efficacy, results have led to debates regarding the relevance to "real-world" practice. In contrast, the pragmatic clinical trial (PCT) investigates whether an intervention is effective by studying it across multiple patient groups and practice settings. Although both types of trial design yield important information, economic trends and public policy challenge us to understand the effectiveness, benefits, and harms of interventions.

An excellent example of a PCT is the National Emphysema Treatment Trial (NETT), which advanced our understanding of which patient population would be best served by lung volume reduction surgery, greatly reducing the number of unnecessary or harmful surgeries in a medically and economically vulnerable patient population. Although RCTs remain the standard for regulatory approval, PCTs are gaining popularity due to the potential for real-world applicability and goal of improving quality and value of health care.

Dr. Rebecca Persinger, FCCP
Vice Chair
Dr. Smita A. Desai, FCCP
Steering Committee Member

Critical Care

Therapeutic hypothermia: Not as cool as previously thought?

Therapeutic hypothermia is advocated by the most recent cardiopulmonary resuscitation guidelines, based on two randomized, controlled trials that demonstrated that mild therapeutic hypothermia for 12 or 24 h improved neurologic outcomes and increased survival in patients with out-of-hospital cardiac arrest.

A very well executed study, recently published in the New England Journal of Medicine (Nielsen et al. *N Engl J Med.* 2013;369 [23] :2197-2206) questions the benefit of therapeutic hypothermia. A total of 939 patients (more than twice the number of patients than the prior studies altogether) were randomized to a temperature of either 33°C or 36°C. The results showed no differences in neurologic outcomes or mortality. In contrast with original trials that excluded patients with non-shockable rhythms, this study included patients with cardiac arrest of presumed cardiac

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cause, irrespective of the initial rhythm. Discontinuation of life support was one of the most common causes of death in prior trials; this problem was addressed by Nielsen with the institution of a strict protocol for discontinuation of life support. Hyperthermia has been associated with unfavorable neurologic outcomes and was present in the normothermia group of previous trials but not in the 36°C arm of the current trial. These findings support the importance of targeted temperature control but challenge the benefit of mild therapeutic hypothermia (33°C); it is likely that the similar outcomes in both groups are due to the active prevention of hyperthermia.

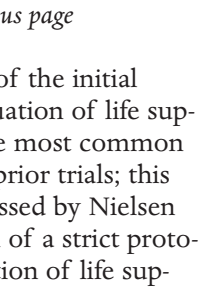
It is evident that active temperature management is associated with better outcomes and hyperthermia must be prevented in these patients. The recommendations for therapeutic hypothermia may need to be revisited.

Dr. Angel O. Coz Yataco, FCCP
Steering Committee Member

Home Care

Barbara Rogers, patient advocate

Barbara Rogers died on December 7, 2013. She was an indefatigable patient advocate. Born in 1947 with scoliosis and a club foot, until age 6, she was never without a cast or brace. At 13, the bone used for her spinal fusion proved infected, and Rogers spent six months in a hospital isolation room. After marriage, she delivered a healthy 7-pound baby boy – although she'd been told she could not survive a pregnancy.



BARBARA ROGERS

During the next 20 years, Rogers was a wife, mother and businesswoman with a grueling schedule. Eventually, she ended up hospitalized in respiratory failure. Dr. Norma Braun, FCCP, became Rogers' pulmonologist and started her on home noninvasive ventilation. For the remainder of her life, Rogers credited Dr. Braun with "keeping her going."

Rogers believed in patient education, and in the mid 1990s, she started "Breethezy," an organization devoted to helping home respiratory patients. In 2000, she started NECA (National Emphysema and COPD Association), recognizing there was a great need for patient advocacy. Rogers lectured on the patient's perspective all over the world and was well-published.

An indefatigable patient advocate, Ms. Rogers believed in patient education, and in the mid 1990s, she started "Breethezy," an organization devoted to helping home respiratory patients.

In 2003, Rogers was the recipient of the Dr. Charles H. Hudson Award for Cardiopulmonary Health, recognizing efforts to positively influence the public's awareness of cardiopulmonary health.

In 2010, Rogers was the first patient to be honored by CHEST with the Margaret Pfrommer Memorial Lecture in Long-term Mechanical Ventilation. The award honors an individual who has advanced mechani-

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cal ventilation and fostered partnerships between physicians and patients.

Angela King, RRT
Steering Committee Member

Donations in Barbara Roger's name will be directed to the Margaret Pfrommer Memorial Lecture. To make your gift, please contact Patti Steele at The CHEST Foundation at 224/927-5202 or by e-mail at psteele@chestnet.org.

Interstitial and Diffuse Lung Disease

Idiopathic interstitial pneumonias 12 years later: How far have we come?

This year, updated guidelines classifying the confounding "alphabet soup" of idiopathic interstitial pneumonias (IIPs) were published by the American Thoracic Society/European Respiratory Society (Travis et al. *Am J Respir Crit Care Med*. 2013;188(6):733-748). The revisions incorporate 12 years of observation, science, and reflections of a multidisciplinary group of pulmonologists, radiologists, and pathologists.

Highlighted significant updates include an upgrade for nonspecific interstitial pneumonia (NSIP) from a provisional diagnosis to an ac-

cepted entity, recognition of the heterogeneity of NSIP and usual interstitial pneumonia (UIP), and added import of acute exacerbations. Pragmatically, understanding the CT scan and bronchoalveolar lavage characteristics of the smoking-related ILD, respiratory bronchiolitis interstitial lung disease (RB-ILD), reduces the need for surgical biopsies. New diagnostic entities are introduced in this classification, and hints of the future are described as biomarkers and genetic underpinnings are discussed.

The difficult task remains as to how to handle the all-too-often observed "unclassified" disease. The authors of the guidelines pay due diligence to this real world concern acknowledging the dilemmas faced by providers and developing a schematic for defining and managing this conundrum based on the clinical disease behavior. Accurately defining clinical behavior may prove challenging as judgment depends on the experience and interpretation of the provider. Standards of care are difficult in this setting and the clinical relevance of this approach remains to be seen.

These new guidelines bring together a decade of advancements made in this confusing group of diseases into a usable roadmap for patient

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CRITICAL CARE COMMENTARY: Palliative care and its role in the ICU

BY DR. EARL L. SMITH AND DR. TITA CASTOR

The ICU is where palliative care may have the greatest impact in a hospital. Hospitalized patients with the highest risk of dying are often found in the ICU. Many are sent to the ICU not only for intensive monitoring but also for life-sustaining treatments. Nevertheless, each year more than 500,000 patients die after ICU admission (Angus et al. *Crit Care Med*. 2004;32[3]:638).

Along with life-sustaining therapies, patients who are seriously ill are in need of symptom management. The ICU is a place of high stress and anxiety where patients and families are faced with difficult decisions. Critical care physicians are charged not only with the care of these very complex patients but also with communicating with families and often

having to deliver bad news.

Looking into the future we face the great challenge of caring for the more than 77 million aging baby boomers. Palliative care will be an invaluable part of health care for the aging population; many will be living with chronic disease, a number needing repeated hospitalizations, and some needing the ICU.

Differences between palliative care and hospice

Many, physicians included, continue to confuse palliative care with hospice care. In the United States, hospice service is offered when life expectancy is less than 6 months and patients and families choose to forgo disease-modifying therapies. Palliative care, in contrast, can be offered in conjunction with disease modifying or curative therapies – it is appropriate for all stages of the disease trajectory. Many of the patients who receive palliative care are not terminally ill. Sadly, the need for palliative care is often not recognized until late, when patients are dying.

Palliative care focuses on the care of the "whole patient," improving quality of life through relief of symptoms whether physical, psychological, or spiritual, as well as providing support for those who surround the patient. Palliative care is provided by an interdisciplinary team that works together with the patient's primary team. Palliative care teams throughout the country differ in their make-up. Optimally, the interdisciplinary team includes physicians, nurses, pastoral care, and social work with specialized training and certification.

Palliative care, in contrast to hospice, can be offered in conjunction with disease modifying or curative therapies – it is appropriate for all stages of the disease trajectory.

Seven key domains have been identified for ICU palliative care. These include symptom management and comfort care, communication, patient- and family-centered decision-making, emotional and practical support for patients and families, spiritual support for patients and families, continuity of care, and emotional and organizational support for ICU clinicians (Nelson, et al. Implementing ICU Screening Criteria for Unmet Palliative Care Needs: A Guide for ICU and Palliative Care Staff 2013. The IPAL-ICU Project, CAPC, http://ipal.capc.org).

ICU screening criteria

Standardized tools to evaluate/screen patients for possible palliative care consult services have been developed (see Nelson, et al.).

There are disease criteria that include diagnoses, such as cancer, multiorgan failure, acute brain injury, and advanced stages of chronic disease. The utilization criteria include prolonged ICU stay, multiple ICU admissions, frequent hospitalizations, admission from long-term care, conversations about life-sustaining treatments, and consideration for ethics consults.

Other criteria to consider are discussion of goals of care, answering yes to the "surprise question," ("Would it surprise you if this patient died in the next 12 months?"), anticipated discharge to long-term acute care, and difficult-to-manage symptoms.

In addition to symptom management, palliative care's focus on im-

Continued on following page

Inhibitors of Cytochrome P450 3A4

The main route of metabolism of corticosteroids, including budesonide, a component of SYMBICORT, is via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4). After oral administration of ketoconazole, a strong inhibitor of CYP3A4, the mean plasma concentration of orally administered budesonide increased. Concomitant administration of CYP3A4 may inhibit the metabolism of, and increase the systemic exposure to, budesonide. Caution should be exercised when considering the coadministration of SYMBICORT with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) [see **WARNINGS AND PRECAUTIONS**].

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

SYMBICORT should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of formoterol, a component of SYMBICORT, on the vascular system may be potentiated by these agents. In clinical trials with SYMBICORT, a limited number of COPD and asthma patients received tricyclic antidepressants, and, therefore, no clinically meaningful conclusions on adverse events can be made.

Beta-Adrenergic Receptor Blocking Agents

Beta-blockers (including eye drops) may not only block the pulmonary effect of beta-agonists, such as formoterol, a component of SYMBICORT, but may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Diuretics

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category C.

There are no adequate and well-controlled studies of SYMBICORT in pregnant women. SYMBICORT was teratogenic and embryocidal in rats. Budesonide alone was teratogenic and embryocidal in rats and rabbits, but not in humans at therapeutic doses. Formoterol fumarate alone was teratogenic in rats and rabbits. Formoterol fumarate was also embryocidal, increased pup loss at birth and during lactation, and decreased pup weight in rats. SYMBICORT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

SYMBICORT

In a reproduction study in rats, budesonide combined with formoterol fumarate by the inhalation route at doses approximately 1/7 and 1/3, respectively, the maximum recommended human daily inhalation dose on a mg/m^2 basis produced umbilical hernia. No teratogenic or embryocidal effects were detected with budesonide combined with formoterol fumarate by the inhalation route at doses approximately 1/32 and 1/16, respectively, the maximum recommended human daily inhalation dose on a mg/m^2 basis.

Budesonide

Studies of pregnant women have not shown that inhaled budesonide increases the risk of abnormalities when administered during pregnancy. The results from a large population-based prospective cohort epidemiological study reviewing data from three Swedish registries covering approximately 99% of the pregnancies from 1995-1997 (ie, Swedish Medical Birth Registry; Registry of Congenital Malformations; Child Cardiology Registry) indicate no increased risk for congenital malformations from the use of inhaled budesonide during early pregnancy. Congenital malformations were studied in 2014 infants born to mothers reporting the use of inhaled budesonide for asthma in early pregnancy (usually 10-12 weeks after the last menstrual period), the period when most major organ malformations occur. The rate of recorded congenital malformations was similar compared to the general population rate (3.8% vs 3.5%, respectively). In addition, after exposure to inhaled budesonide, the number of infants born with orofacial clefts was similar to the expected number in the normal population (4 children vs 3.3, respectively).

These same data were utilized in a second study bringing the total to 2534 infants whose mothers were exposed to inhaled budesonide. In this study, the rate of congenital malformations among infants whose mothers were exposed to inhaled budesonide during early pregnancy was not different from the rate for all newborn babies during the same period (3.6%).

Budesonide produced fetal loss, decreased pup weight, and skeletal abnormalities at subcutaneous doses in rabbits less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis and in rats at doses approximately 6 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis. In another study in rats, no teratogenic or embryocidal effects were seen at inhalation doses up to 3 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis.

Experience with oral corticosteroids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans.

Formoterol

Formoterol fumarate has been shown to be teratogenic, embryocidal, to increase pup loss at birth and during lactation, and to decrease pup weights in rats when given at oral doses 1400 times and greater the maximum recommended human daily inhalation dose on a mcg/m^2 basis. Umbilical hernia was observed in rat fetuses at oral doses 1400 times and greater the maximum recommended human daily inhalation dose on a mcg/m^2 basis. Brachygnathia was observed in rat fetuses at an oral dose 7000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis. Pregnancy was prolonged at an oral dose 7000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis. In another study in rats, no teratogenic effects were seen at inhalation doses up to 500 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis.

Subcapsular cysts on the liver were observed in rabbit fetuses at an oral dose 54,000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis. No teratogenic effects were observed at oral doses up to 3200 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis.

Nonteratogenic Effects

Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Labor and Delivery

There are no well-controlled human studies that have investigated the effects of SYMBICORT on preterm labor or labor at term. Because of the potential for beta-agonist interference with uterine contractility, use of SYMBICORT for management of asthma during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

Nursing Mothers

Since there are no data from controlled trials on the use of SYMBICORT by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue SYMBICORT, taking into account the importance of SYMBICORT to the mother.

Budesonide, like other corticosteroids, is secreted in human milk. Data with budesonide delivered via dry powder inhaler indicates that the total daily oral dose of budesonide available in breast milk to the infant is approximately 0.3% to 1% of the dose inhaled by the mother [see **CLINICAL PHARMACOLOGY, Pharmacokinetics** in full Prescribing Information (12.3)]. For SYMBICORT, the dose of budesonide available to the infant in breast milk, as a percentage of the maternal dose, would be expected to be similar.

In reproductive studies in rats, formoterol was excreted in the milk. It is not known whether formoterol is excreted in human milk.

Pediatric Use

Safety and effectiveness of SYMBICORT in asthma patients 12 years of age and older have been established in studies up to 12 months. In the two 12-week, double-blind, placebo-controlled US pivotal studies 25 patients 12 to 17 years of age were treated with SYMBICORT twice daily [see **CLINICAL STUDIES** in full Prescribing Information (14.1)]. Efficacy results in this age group were similar to those observed in patients 18 years and older. There were no obvious differences in the type or frequency of adverse events reported in this age group compared with patients 18 years of age and older.

The safety and effectiveness of SYMBICORT in asthma patients 6 to <12 years of age has not been established.

Overall 1447 asthma patients 6 to <12 years of age participated in placebo- and active-controlled SYMBICORT studies. Of these 1447 patients, 539 received SYMBICORT twice daily. The overall safety profile of these patients was similar to that observed in patients ≥12 years of age who also received SYMBICORT twice daily in studies of similar design.

Controlled clinical studies have shown that orally inhaled corticosteroids including budesonide, a component of SYMBICORT, may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of HPA-axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA-axis function. The long-term effect of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final height are unknown. The potential for "catch-up" growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied.

In a study of asthmatic children 5-12 years of age, those treated with budesonide DPI 200 mcg twice daily (n=311) had a 1.1 centimeter reduction in growth compared with those receiving placebo (n=418) at the end of one year; the difference between these two treatment groups did not increase further over three years of additional treatment. By the end of 4 years, children treated with budesonide DPI and children treated with placebo had similar growth velocities. Conclusions drawn from this study may be confounded by the unequal use of corticosteroids in the treatment groups and inclusion of data from patients attaining puberty during the course of the study.

The growth of pediatric patients receiving orally inhaled corticosteroids, including SYMBICORT, should be monitored. If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect should be considered. The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained. To minimize the systemic effects of orally inhaled corticosteroids, including SYMBICORT, each patient should be titrated to the lowest strength that effectively controls his/her asthma [see **DOSAGE AND ADMINISTRATION**].

Geriatric Use

Of the total number of patients in asthma clinical studies treated with SYMBICORT twice daily, 149 were 65 years of age or older, of whom 25 were 75 years of age or older.

In the COPD studies of 6 to 12 months duration, 349 patients treated with SYMBICORT 160/4.5 twice daily were 65 years old and above and of those, 73 patients were 75 years of age and older. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

As with other products containing beta$_2$-agonists, special caution should be observed when using SYMBICORT in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by beta$_2$-agonists.

Based on available data for SYMBICORT or its active components, no adjustment of dosage of SYMBICORT in geriatric patients is warranted.

Hepatic Impairment

Formal pharmacokinetic studies using SYMBICORT have not been conducted in patients with hepatic impairment. However, since both budesonide and formoterol fumarate are predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of budesonide and formoterol fumarate in plasma. Therefore, patients with hepatic disease should be closely monitored.

Renal Impairment

Formal pharmacokinetic studies using SYMBICORT have not been conducted in patients with renal impairment.

OVERDOSAGE

SYMBICORT

SYMBICORT contains both budesonide and formoterol; therefore, the risks associated with overdosage for the individual components described below apply to SYMBICORT. In pharmacokinetic studies, single doses of 960/54 mcg (12 actuations of SYMBICORT 80/4.5) and 1280/36 mcg (8 actuations of 160/4.5), were administered to patients with COPD. A total of 1920/54 mcg (12 actuations of SYMBICORT 160/4.5) was administered as a single dose to both healthy subjects and patients with asthma. In a long-term active-controlled safety study in asthma patients, SYMBICORT 160/4.5 was administered for up to 12 months at doses up to twice the highest recommended daily dose. There were no clinically significant adverse reactions observed in any of these studies.

Clinical signs in dogs that received a single inhalation dose of SYMBICORT (a combination of budesonide and formoterol) in a dry powder included tremor, mucosal redness, nasal catarrh, redness of intact skin, abdominal respiration, vomiting, and salivation; in the rat, the only clinical sign observed was increased respiratory rate in the first hour after dosing. No deaths occurred in rats given a combination of budesonide and formoterol at acute inhalation doses of 97 and 3 mg/kg, respectively (approximately 1200 and 1350 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). No deaths occurred in dogs given a combination of budesonide and formoterol at the acute inhalation doses of 732 and 22 mcg/kg, respectively (approximately 30 times the maximum recommended human daily inhalation dose of budesonide and formoterol on a mcg/m^2 basis).

Budesonide

The potential for acute toxic effects following overdose of budesonide is low. If used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism may occur [see **WARNINGS AND PRECAUTIONS**]. Budesonide at five times the highest recommended dose (3200 mcg daily) administered to humans for 6 weeks caused a significant reduction (27%) in the plasma cortisol response to a 6-hour infusion of ACTH compared with placebo (+1%). The corresponding effect of 10 mg prednisone daily was a 35% reduction in the plasma cortisol response to ACTH.

In mice, the minimal inhalation lethal dose was 100 mg/kg (approximately 600 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). In rats, there were no deaths following the administration of an inhalation dose of 68 mg/kg (approximately 900 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). The minimal oral lethal dose in mice was 200 mg/kg (approximately 1300 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis) and less than 100 mg/kg in rats (approximately 1300 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

Formoterol

An overdose of formoterol would likely lead to an exaggeration of effects that are typical for beta$_2$-agonists: seizures, angina, hypertension, hypotension, tachycardia, atrial and ventricular tachyarrhythmias, nervousness, headache, tremor, palpitations, muscle cramps, nausea, dizziness, sleep disturbances, metabolic acidosis, hyperglycemia, hypokalemia. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of formoterol. No clinically significant adverse reactions were seen when formoterol was delivered to adult patients with acute bronchoconstriction at a dose of 90 mcg/day over 3 hours or to stable asthmatics 3 times a day at a total dose of 54 mcg/day for 3 days.

Treatment of formoterol overdosage consists of discontinuation of the medication 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 medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of formoterol. Cardiac monitoring is recommended in cases of overdosage.

No deaths were seen in mice given formoterol at an inhalation dose of 276 mg/kg (more than 62,200 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). In rats, the minimum lethal inhalation dose was 40 mg/kg (approximately 18,000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). No deaths were seen in mice that received an oral dose of 2000 mg/kg (more than 450,000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). Maximum nonlethal oral doses were 252 mg/kg in young rats and 1500 mg/kg in adult rats (approximately 114,000 times and 675,000 times the maximum recommended human inhalation dose on a mcg/m^2 basis).

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Continued from previous page

proving the patients' quality of life includes support to families and to the health-care providers in the ICU, who also confront complex life-and-death decisions. Consequently, palliative care is consistent with the goals of hospitals to improve the management of symptoms, such as pain, improving patient and family satisfaction, and reducing length of stay.

The availability of palliative care services to patients is improving. Palliative care services are usually not self-sustaining; billing provides some support but services usually require support from administration or philanthropy; this is offset by the cost-savings provided (Morrison et al. *Arch Intern Med*. 2008;168[16]:1783).

Recognition of the need for palliative care has led to the rise in the number of hospitals that provide the service to 63% of those with 50 or more beds (capc.org/reportcard/). Many organizations recognize the importance of palliative care services. Hospitals can now obtain Advanced Certification in Palliative Care from The Joint Commission, and the Committee on Cancer has made the availability of palliative care a requirement for certification as a cancer center. States such as New York have passed laws in an effort to ensure patients are offered and have access to palliative care.

Symptom management in the ICU

Patients in the ICU can experience a gamut of symptoms that require the expertise of a palliative care team. Palliative care practitioners receive comprehensive training into the mechanism and action of drugs used to control pain, anxiety, delirium, and more. Some patients may require patient-controlled analgesia or opioid-sparing strategies, such as adjuvant pain medications or interventional procedures. The side effects of treatment are included in the symptom management provided by a palliative care specialist, for example, constipation, dry mouth, and opioid-induced neurotoxicity.

Because of their skill-set, palliative care team members can help bring clarity and provide support. This may help prevent burnout among critical care physicians and nurses.

Need for interdisciplinary team

Patients and families experience high rates of anxiety, depression, and posttraumatic stress symptoms within a week of ICU admission (Paparrigopoulos et al. *J Psychosom Res*. 2006;61[5]:719). Among bereaved families of patients who died in medical intensive care units, one-third had depression, anxiety, panic, or complicated grief (Siegel et al. *Crit Care Med*. 2008; 36[6]:1722). The palliative care team can aid with communication with families and help provide extra support. Families and patients frequently need multiple conversations to understand the ramifications of life and death decisions. The palliative care team can provide expertise in prognostication and end-of-life care that may help families and clinicians with decision-making about therapies. Certified palliative care health-care workers receive specialized training in communication strategies. Patients and their families may feel more comfortable discussing certain topics with a nurse, social worker, or chaplain. This may range from the mundane (eg, insurance issues) to complex social or psychological issues. The palliative care team can identify problems and refer to support services.

Continuity and care transitions

The palliative care team can help to maintain the plan of care when the patient transitions from the ICU to a stepdown unit or regular medical floor. The team usually stays with a patient until the patient leaves the hospital, across multiple admissions. Many patients experience chronic illness and other sequelae after leaving the ICU, leading to loss of function and quality of life. Continuity provided by a consult team can help patients and families cope with such circumstances. The interdisciplinary team can be an institutional memory for medical and psychosocial goals-of-care and can help with discharge planning, thus reducing the hospital readmission rate. Palliative care supports the patient's and family's goals, whether for home, skilled nursing facility (SNF), hospice, repatriation to country of origin, or other situations.

Support for ICU clinicians

When patient goals of care are unclear, and staff and families are considering limitations on life-supporting treatments, conflict can arise within the ICU team about decision-making and other issues (Breen et al. *J Gen Intern Med*. 2001;16[5]:283). Because of their experience and skill-set, palliative care team members can help bring clarity and provide support. This may help prevent burnout among critical care physicians and nurses.

It can be argued that admission to ICU for many with life-limiting conditions is a systems failure.

In an ideal system, goals of care would have been addressed and possibly prevent many of these ICU admissions. For example, the patient with severe Parkinson's disease would have had a conversation with his neurologist about whether or not he desires intubation for aspiration pneumonia before the question becomes an emergency. This would spare a family the burden of having to make decisions without really knowing the patient's wishes. In many hospital systems, addressing goals of care is mandatory before beginning life-prolonging therapies if the patient has a limited life expectancy. For the reasons discussed previously, palliative care should be a key collaborative part of care in the ICU.

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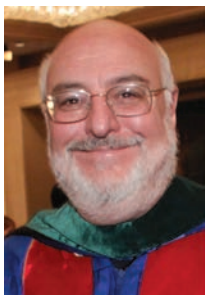
EDITOR'S COMMENT

As the demand for critical care rises and the shortage of providers becomes more pronounced, there is an ever-increasing need for palliative critical care.



In this solid and insightful review, Drs. Castor and Smith provide a clear delineation of palliative care and its growing importance in the ICU. As we strive for appropriate outcomes and use of precious resources, a solid collaboration between palliative care and critical care is truly important.

As we always try to do what is best, that is not always clearly defined. Palliative care can help us sort through these difficult issues and try to come out with what is truly best for the patient, the family, and even the caregivers.

Dr. Peter Spiro, FCCP
Section Editor
for Critical Care Commentary

It's all about the guidelines (part 3 of 3)

BY BRENDA EDWARDS, CPC, CPMA, CPC-I, CEMC

The general guidelines in ICD-10-CM are intended to provide overall guidance on usage of the code set. These guidelines are similar to those in ICD-9-CM, with a few exceptions. Let's take a look at some of these general guidelines.

The guidelines are located in Section 1.B of the ICD-10-CM code book. There is a general statement made at the beginning of the section regarding hierarchy of application of the guidelines. It states, "The conventions and instructions of the classification take precedence over guidelines." This means that if the general guidelines give a certain instruction (eg, sequencing rules), but the Tabular Index gives a different instruction for a specific category or code block, then the instruction in the Tabular Index should be followed.

Other general ICD-10-CM guidelines worth noting:

1.B.13 – Laterality: This is a new guideline because bilateral codes do not exist in ICD-9-CM. The guideline states that if no bilateral code exists and the condition is bilateral, two codes must be assigned (one for right and one for left) to report the complete condition. For example, if a patient has bilateral carpal tunnel syndrome, codes **G56.01 Carpal tunnel, right upper limb code** and **G56.02 Carpal tunnel, left upper limb** would need to be assigned since the codes for carpal tunnel syndrome do not include a bilateral code.

1.B.16 – Documentation of Complications of Care: This guideline gives direction regarding the requirements for a condition to be reported as a complication of care. It states that code assignment is based on the provider's documentation of a cause-and-effect relationship between the care provided and the condition, which results in a complication. Discussions with physicians and other providers regarding specifics of their documentation are important to show the complexity of a patient's case.

The guideline also states that if the documentation is not clear as to the relationship, the physician or other provider should be queried for clarification.

1.B.17 – Borderline Diagnosis: If a physician or other provider documents a condition as being borderline at the time of discharge, there are two choices (below).

This guideline applies to inpatient or outpatient discharges. If the documentation is unclear, the guidelines again state to query the provider of service for clarification.

► If the term "Borderline" is referenced in the Alphabetic Index and there is an entry for the specified borderline condition, then the condition is coded. For example, borderline diabetes has a listed code in the Alphabetic Index of **R73.09 Other abnormal glucose**.

► If there is no entry, the condition is coded as if it exists.

1.B.18 – Use of Signs/Symptoms/Unspecified Codes: This new guideline addresses the use of signs, symptoms, and unspecified codes. It states that unspecified codes have acceptable uses and are necessary at times, and that each encounter should be coded to the level of certainty known for that encounter. Signs and symptoms are appropriate to report when a definitive diagnosis has not been established at the end of the encounter. If sufficient clinical information is unknown or unavailable (eg, if you're waiting on lab results), it is acceptable to report an unspecified code. The guideline further states, "Unspecified codes should be reported when they are the codes that most accurately reflect what is known about the patient's condition at the time of that particular encounter." The final instruction regarding correct code assignment states it would be inappropriate to assign a more specific diagnosis code not supported by documentation. It is also inappropriate to order additional diagnostic testing to determine a more specific diagnosis code.

If the general guidelines give a certain instruction but the Tabular Index gives a different instruction for a specific category or code block, then the instruction in the Tabular Index should be followed.

It is a good idea to become familiar with all guidelines before the go-live date for ICD-10-CM, October 1, 2014. We are less than 1 year away from implementation and you can never be too prepared.

This is the third part of a series examining the complexities of the ICD-10-CM. For parts 1 and 2, see articles in the December 2013 and January 2014 editions of CHEST *Physician or go to chestnet.org/publications.*

Brenda Edwards entered the coding and billing profession 25 years ago, and has been involved in many aspects of the field. Her current responsibilities include chart auditing, coding and compliance education, and contributing articles to AAPC and industry publications. Brenda is an AAPC ICD-10-CM trainer and has presented for AAPC workshops, regional conferences, and local chapter meetings. She has also served on the AAPCCA local chapter board of directors.

Physician Payment Sunshine Act: Take charge of your info needs

BY ED DELLERT, RN, MBA, CCMEP

Senior Vice President Clinical Education, Informatics, and Research

If you did not see the 2013 awareness article on the implementation of the Physician Payment Sunshine Act in *CHEST Physician,* it might be worth your while to learn more about the act and how to manage your information. Here are a few steps to consider:

1. Sign up with CMS to receive updates to open access updates. Go to cms.gov/Regulations-and-Guidance/Legislation/National-Physician-Payment-Transparency-Program/Contact-Us.html.

2. Review and update your information associated with your National Provider Identifier number. Go to cms.gov/Regulations-and-Guidance/Legislation/National-Physician-payment-Transparency-Program/Physicians.

3. Technology savvy? Take advantage of the mobile app to help in tracking open payments. Go to cms.gov/Regulations-and-Guidance/Legislation/National-Physician-Payment-Transparency-Program/Physicians.

Hope these resources help you in your efforts related to open payments associated with the Physician Payment Sunshine Act.

This Month in *CHEST:* Editor's Picks

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

Disturbed Intestinal Integrity in Patients With COPD: Effects of Activities of Daily Living. *By Dr. E. Rutten et al.*

Measurement of Activities of Daily Living in Patients With COPD: A Systematic Review. By Dr. T. Janaudis-Ferreira et al.

Importance of *Legionella pneumophila* in the Etiology of Severe Community-Acquired Pneumonia in Santiago, Chile. *By Dr. F. Arancibia et al.*

***EIF2AK4* Mutations in Pulmonary Capillary Hemangiomatosis.** *By Dr. D. H. Best et al.*

POINT/COUNTERPOINT
Should Medicare Allow Respiratory Therapists to Independently Practice and Bill for Educational Activities Related to COPD?
Yes: *Drs. T. M. Fuhrman and R. Aranson*
No: *Drs. K. Courtright and S. Manaker*

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care. The unclassified IIPs remain our challenge and herald another decade of progress.

Dr. Mary Beth Scholand, FCCP
Steering Committee Member

Airways Disorders

Once-daily inhaled therapy for COPD

Most randomized controlled trials demonstrate that once-daily bronchodilators are more effective than twice-daily bronchodilators in improving lung function and patient-reported outcomes. Several once-daily inhaled medications have been approved to treat patients with COPD or await a decision by the European Medicines Agency (EMA) and/or the US Food and Drug Administration (FDA). The balance of expected benefits and possible side effects should be considered for each patient before prescribing these medications.

Once-daily long-acting beta-agonists (LABA)

► Indacaterol approved by EMA (150 and 300 micrograms) and FDA (75 micrograms).

► Olodaterol (5 micrograms) is approved in Canada, some European countries, and Russia. On January 29, 2013, the Pulmonary-Allergy Drugs Advisory Committee (PADAC) to the FDA voted 15 to 1 in support of this medication.

Once-daily long-acting muscarinic-antagonists (LAMA)

► Tiotropium delivered by soft mist inhaler is under review by the FDA.

► Glycopyrronium (50 micrograms) is approved by EMA and in Japan.

Most randomized controlled trials demonstrate that once-daily bronchodilators are more effective than twice-daily bronchodilators in improving lung function and patient-reported outcomes.

Once-daily dual LABA/LAMA

► Indacaterol/glycopyrronium (110/50 micrograms) approved by EMA and in Japan.

► Umeclidinium-Vilanterol (62.5/25 micrograms) approved by the FDA on December 18, 2013.

Once-daily inhaled corticosteroid/LABA

► Fluticasone furoate/vilanterol (100/25 micrograms) approved by the FDA in May 2013 for "Maintenance treatment of airflow obstruction and to reduce exacerbations of COPD in those with a history of exacerbations."

Boxed warning for LABAs

► Once-daily indacaterol and medications containing vilanterol have a boxed warning that LABAs increase the risk of asthma-related deaths.

► Filing of additional dual bronchodilators (LABA/LAMA) and ICS/LABA combinations used once or twice daily is expected over the next few years.

Dr. Donald A. Mahler, FCCP
Steering Committee Member

CLASSIFIEDS

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Established Los Angeles group seeking BE/BC Pulmonologist.

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email cv to **lapulmonaryjob@gmail.com**

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donohueandassoc@aol.com

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CALIFORNIA

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Kimberly Salvail, Huntsville Hospital –
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or 256-265-7073.

Alabama

Forbes Top Ten Smartest City Seeks a Pulm/CC Physician Immediately!

- Established, four physician practice
- Highly competitive salary w/productivity incentive
- Partnership track w/401k, paid vacation and CME allowance
- 1:5 Call
- EMR
- 101 open ICU beds
- 881 bed Level I Trauma/ Regional Referral Center

Interested physicians should contact:
Kimberly Salvail, Huntsville Hospital –
kimberly.salvail@hhsys.org
or 256-265-7073.

Colorado

Colorado Health Medical Group is seeking a Pulmonologist/Critical Care/Sleep Medicine trained physician. Will rotate in the hospital and our Loveland based clinic. Call is 1:11 nights and 1:5-6 weekends. Physician will be doing general Pulm/CC procedures and read sleep studies from outlying facilities. Group is starting a home based sleep study program.

If interested, email your CV to
Kelley.Hekowczyk@uchealth.org

Tennessee

Pulmonary Program Director James H. Quillen College of Medicine seeks candidates at the Associate/Full Professor level with M.D. and active ABIM certification in Pulmonary and Critical Care Medicine to serve as Fellowship Director. Candidates must have an established record of scholarship and mentoring of junior faculty. ETSU is an AA/EOE employer.

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CPAP treats resistant hypertension in OSA patients

BY MARY ANN MOON
Frontline Medical News

For patients who have resistant hypertension and obstructive sleep apnea, 3 months of treatment with continuous positive airway pressure significantly reduces mean and diastolic blood pressure and improves the nocturnal blood pressure pattern, according to a report published in JAMA.

These improvements are dose related, with mean blood pressure decreasing 1.3 mm Hg, systolic blood pressure decreasing 1.9 mm Hg, and diastolic blood pressure decreasing 1.0 mm Hg for every additional hour of CPAP use, said Dr. Miguel-Angel Martinez-Garcia of the respiratory department at Hospital Universitario y Politecnico La Fe, Valencia (Spain), and his associates.

"International guidelines have pointed out that even minimal reductions in blood pressure levels (to the order of 2-3 mm Hg of systolic pressure) could have a clinically significant effect by greatly reducing subsequent cardiovascular mortality (between 6% and 8% for stroke and 4% and 5% for coronary heart disease)," Dr. Martinez-Garcia and his colleagues noted.

Previous studies have shown that CPAP produces clinically significant decreases in blood pressure levels, but all have had "significant methodological limitations such as small cohorts or lack of randomization." So Dr. Martinez-Garcia and his associates performed a large randomized multicenter clinical trial to assess the issue.

They identified 194 adults treated at 24 teaching hospitals across Spain who had resistant hypertension unrelated to known causes such as primary aldosteronism, renal artery stenosis, or renal insufficiency. Resistant hypertension was confirmed via 24-hour ambulatory blood pressure monitoring. The study subjects also had obstructive sleep apnea, which was confirmed by standard sleep studies.

These subjects were randomly assigned to receive CPAP (98 patients) or no intervention (96 patients) while continuing their usual regimens of antihypertensive treatment. Approximately 69% of the subjects were men; mean age was 56 years, mean body mass index was 34.1, mean number of antihypertensive drugs taken was 3.8, and mean apnea-hypopnea index was 40.4 events per hour.

In the intention-to-treat analysis, after 3 months, the CPAP group achieved significantly greater decreases in 24-hour mean blood pressure and 24-hour mean diastolic blood pressure, and showed greater improvements during the night than during daytime. It also converted to more favorable nocturnal "dipper" and "riser" patterns in blood pressure, indicating decreased cardiovascular risk.

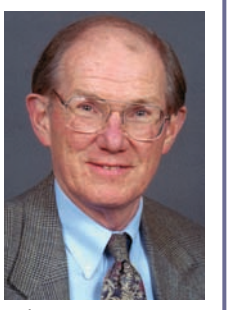
In the per-protocol analysis involving the 71 CPAP patients and 87 controls who adhered to the study protocol, these improvements were even more pronounced: The CPAP group showed a significant 4.4–mm HG decrease in 24-hour mean blood pressure, a 4.9–mm Hg decrease in systolic blood pressure, and a 4.1–mm Hg decrease in diastolic blood pressure (JAMA 2013 Dec. 10 [doi:10.1001/jama.2012.281250]).

At night, the findings were even better, with a 7.1–mm Hg decrease in systolic blood pressure and 4.1–mm Hg decrease in diastolic blood pressure. And again, the CPAP patients were more likely to convert to more favorable nocturnal "dipper" and "riser" patters in blood pressure.

There also was a positive linear correlation between the number of hours of CPAP use per night and the decrease in 24-hour mean blood pressure and diastolic blood pressure.

This study was supported by Philips Respironics, Sociedad Espanola de Neumologia, Instituto de Salud Carlos III, and Sociedad Valencia de Neumologia. No other conflicts of interest were reported.

VIEW ON THE NEWS



Dr. Paul A. Selecky, FCCP, comments: This report adds weight to the 2008 American Heart Association Scientific Statement on resistant hypertension, which stated that untreated sleep apnea is a secondary cause of resistant hypertension (Circulation 2008;117:e510-26). The present report takes the next step of showing that treatment with CPAP improves the hypertension.

CPAP alternative? Implantable device cut OSA severity

BY MARY ANN MOON
Frontline Medical News

An implantable device that stimulates the upper airway nerves and muscles produced long-term, clinically meaningful reductions in the severity of obstructive sleep apnea in an industry-sponsored study reported in the New England Journal of Medicine.

One year after implantation, patients showed a 68% reduction in scores on the Apnea-Hypopnea Index (AHI) and a 70% reduction in scores on the Oxygen Desaturation Index (ODI), as well as subjective improvements in daytime sleepiness and quality of life. The magnitude of these benefits was similar to that reported for continuous positive airway pressure (CPAP) therapy and superior to that reported for uvulopalatopharyngoplasty, said Dr. Patrick J. Strollo Jr., FCCP, of the department of otolaryngology, University of Pittsburgh Medical Center and his associates in the STAR (Stimulation Therapy for Apnea Reduction) trial group.

Upper airway stimulation using implanted electrodes to stimulate the hypoglossal nerve on one side of the neck "has been developed as a possible treatment option" for moderate to severe obstructive sleep apnea "and has shown promise in feasibility trials," the investigators noted.

For their study, designed in collaboration with the sponsor (Inspire Medical Systems) and the Food and Drug Administration, 126 patients who couldn't tolerate CPAP therapy underwent surgical implantation of the device and were followed for 1 year. Otolaryngologists at 22 academic and private medical centers performed the surgery, which took a median of 140 minutes (range, 65-360 minutes).

Most (83%) of the participants were men. The mean age was 55 years (range, 31-80 years), and the mean body mass index was 28.4 kg/m^2 (range, 18.4-32.5). The primary outcome of the study was the change in severity of obstructive sleep apnea, as measured by scores on the AHI and the ODI, at 12 months. The median AHI score decreased 68%, from 29.3 events per hour to 9.0 events per hour. The median ODI score dropped 70%, from 25.4 events per hour to 7.4 events per hour, the investigators said (N. Engl. J. Med. 2014 [doi:10.1056/NEJMoa1308659]).

Two-thirds of the participants showed a reduction of at least 50% in AHI score, and three-quarters showed a reduction of at least 25% in ODI score. And the median percentage of sleep time spent with poor oxygen saturation (less than 90%) declined from 5.4% to 0.9%.

In addition, patients' scores on the Functional Outcomes of Sleep Questionnaire, which measures disease-specific quality of life, showed clinically meaningful improvement. And scores on the Epworth Sleepiness Scale normalized.

In the final, "challenge," phase of this study, the first 46 consecutive patients who had responded to this treatment at 1 year were randomly assigned to either continue it (turn the devices on at night) or to discontinue it (turn the devices off at night) for 1 more week. This challenge demonstrated that the improvements in OSA were in fact from the use of the hypoglossal-stimulation device, as sleep apnea relapsed in the patients who discontinued treatment.

There were no serious procedural complications, no rehospitalizations, and no infections. Two patients developed serious device-related adverse events, for an overall rate of less than 2%. In both cases, the device caused discomfort that was resolved by a second surgery to reposition it. Nonserious adverse events – including sore throat from intubation during the procedure, pain at the incision sites, and muscle soreness – occurred in 88% of the study subjects. "This approach may not be appropriate for persons with excessive airway collapsibility," Dr. Strollo and his associates cautioned.

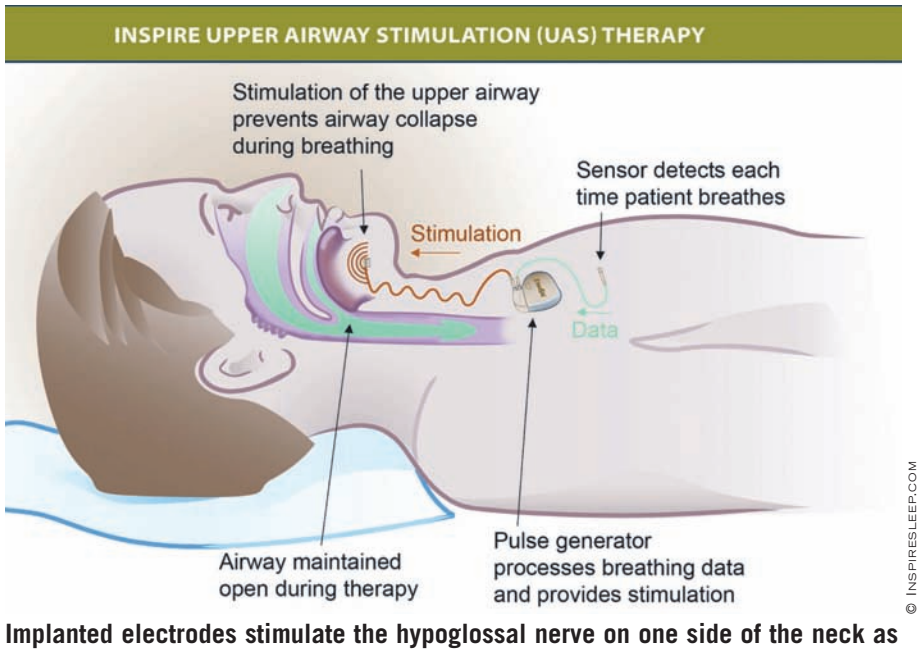
The Food and Drug Administration's Anesthesiology and Respiratory Therapy Devices Panel of the Medical Devices Advisory Committee will discuss, make recommendations, and vote on information related to the premarket approval application on Feb. 20.

VIEW ON THE NEWS

The findings by Strollo et al. give clinicians the rationale to consider hypoglossal nerve stimulation for selected patients who have trouble with CPAP therapy, said Dr. Atul Malhotra, FCCP.

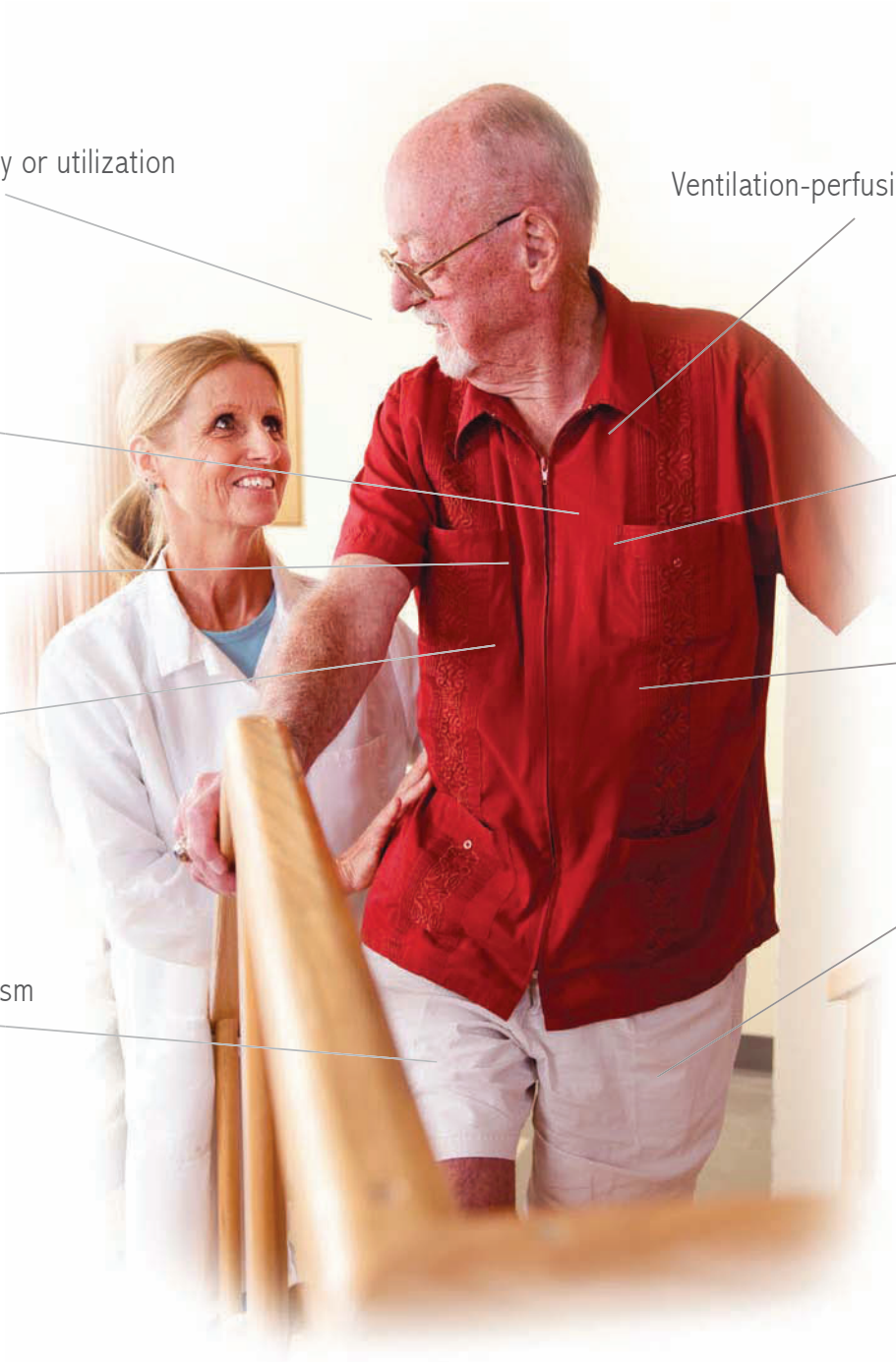
Given the pathophysiology of OSA, a substantial proportion of patients would probably benefit from this treatment, even though symptoms were only reduced rather than completely eradicated. "Although the elimination of apnea would clearly be desirable, the observed reductions are probably similar to the benefits observed with CPAP, particularly when one considers the variability of adherence to CPAP therapy," he said.

Dr. Malhotra is in the division of pulmonary and critical care medicine at the University of California, San Diego. He reported previous ties to Philips Respironics, Apnex, and Apnicure. These remarks were taken from his editorial accompanying Dr. Strollo's report (N. Engl. J. Med. 2014 [doi:10.1056/NEJMe1314084]).



Implanted electrodes stimulate the hypoglossal nerve on one side of the neck as a possible treatment option for moderate to severe obstructive sleep apnea.

Why is this patient short of breath?



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