Aldosterone agonists earn new respect in HF guidelines

Cuts seen in hospitalizations, mortality.

**BY BRUCE JANCIN**

Frontline Medical News

SNOWMASS, COLO. – The latest heart failure guidelines from the American College of Cardiology/American Heart Association place a new emphasis on aldosterone antagonists as a central aspect of the management of symptomatic or previously symptomatic heart failure with reduced ejection fraction – while underscoring important caveats to their use. Aldosterone antagonist therapy earns the strongest possible designation in the guidelines: a Class I/Level of Evidence A recommendation. This is based on data from multiple randomized trials showing that, used appropriately, these agents result in a 30% relative risk reduction in mortality and a 35% reduction in the relative risk of heart failure hospitalization, with a number needed to treat for 36 months of just six patients to prevent one additional death. Those figures place the aldosterone antagonists on a par with the other Class I/A heart failure medications – beta-blockers, ACE inhibitors or angiotensin receptor blockers, and hydralazine/isosorbide dinitrate in African Americans.

See Guidelines • page 9

Low vitamin D – poor ICU outcomes

**BY PATRICE WENDLING**

Frontline Medical News

NAPLES, FLA. – Vitamin D deficiency is common in critically ill trauma patients and portends worse outcomes, a retrospective study suggests. Among 200 trauma patients with available vitamin D levels, 26% were vitamin D deficient on ICU admission. “These patients have a higher APACHE II score, have a longer ICU stay, and will likely be hospitalized greater than 2 weeks,” Dr. Joseph Ibrahim reported at the annual scientific assembly of the Eastern Association for the Surgery of Trauma. Long known to be essential for bone development and wound healing, recent studies have demonstrated that vitamin D deficiency is...
The treatment of pulmonary arterial hypertension (PAH, WHO Group I)

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

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

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

Important Safety Information

**Boxed Warning: Embryo-Fetal Toxicity**

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

**Contraindications**

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

**Warnings and Precautions**

Embryo-fetal Toxicity and OPSUMIT REMS Program

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

Notable requirements of the OPSUMIT REMS Program include:

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

Hepatotoxicity

- Other ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. The incidence of elevated aminotransferases in the SERAPHIN study >3 × ULN were 3.4% for OPSUMIT vs 4.5% for placebo, and >8 × ULN were 2.1% vs 0.4%, respectively. Discontinuations for hepatic adverse events were 3.3% for OPSUMIT vs 1.6% for placebo.
- Obtain liver enzyme tests prior to initiation of OPSUMIT and repeat during treatment as clinically indicated.
- Advise patients to report symptoms suggesting hepatic injury (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching).
- If clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2 × ULN, or by clinical symptoms of hepatotoxicity, discontinue OPSUMIT. Consider re-initiation of OPSUMIT.
when hepatic enzyme levels normalize in patients who have not experienced clinical symptoms of hepatotoxicity.

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

Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)
Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue OPSUMIT.

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

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

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

Please see Brief Summary of Prescribing Information, including BOXED WARNING for embryo-fetal toxicity, on adjacent pages.
**OPSUMIT** (macitentan) CHEST_4.indd   1

### 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 1 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 II) to delay disease progression. Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanooids, 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 prostanooids. Patients had idiopathic or 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. 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)).
- Pharmacists 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 1-866-229-3546. Information on OPSUMIT certified pharmacies or wholesale distributors is available through ActelionPathways at 1-866-229-3546.

### OPSUMIT® (macitentan) CHEST_4.indd   1

**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

<table>
<thead>
<tr>
<th>Aminotransferase Levels</th>
<th>OPSUMIT 10 mg (N=242)</th>
<th>Placebo (N=249)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3 x ULN</td>
<td>3.4%</td>
<td>4.5%</td>
</tr>
<tr>
<td>&gt;6 x ULN</td>
<td>2.1%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

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 x 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.

**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 3.8 years with a median exposure of about 2 years (N=542 for 1 year; N=429 for 2 years; and N=38 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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>OPSUMIT 10 mg (N=242)</th>
<th>Placebo (N=249)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>13%</td>
<td>3%</td>
</tr>
<tr>
<td>Nasopharyngitis/pharyngitis</td>
<td>20%</td>
<td>13%</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>12%</td>
<td>8%</td>
</tr>
<tr>
<td>Headache</td>
<td>14%</td>
<td>9%</td>
</tr>
<tr>
<td>Influenza</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>9%</td>
<td>6%</td>
</tr>
</tbody>
</table>

### 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 P450 treatment options when strong CYP3A4 inhibitors are needed as part of HIV treatment [see Clinical Pharmacology (Pharmacokinetics)].

USE IN SPECIFIC POPULATIONS

Pregnancy

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. No adverse effect 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 women receiving 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 (intravaginal devices [IUD], contraceptive implants or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a patient’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 (Generated 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 (8 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 (Ccr 15-29 ml/min) compared to healthy subjects was increased by 30% and 85%, respectively. This increase is not considered clinically relevant.

Hepatic impairment: Exposure to macitentan was decreased by 21%, 34%, and 8% 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.

Pharmacodynamics

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.

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 is studied in healthy subjects and are shown in Figure 1 below.

Figure 1

<table>
<thead>
<tr>
<th>Interacting drug</th>
<th>Macitentan</th>
<th>Active metabolite</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil</td>
<td>AUC∞+</td>
<td>AUC∞+</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Cilnidipine</td>
<td>AUC∞+</td>
<td>AUC∞+</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>AUC∞+</td>
<td>AUC∞+</td>
<td>Avoid</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>AUC∞+</td>
<td>AUC∞+</td>
<td>Avoid</td>
</tr>
</tbody>
</table>

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 rivaroxaban or their effect on international normalized ratio (INR).

Sildenafil: At steady-state, the exposure to sildenafil 20 mg 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- 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 dilation 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 15- 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 live findings in long-term studies conducted in mice, rats, and dogs at exposures of 12- to 118-fold the human exposure.

Manufactured for:
Actslen Pharmaceuticals US, Inc.
500 Shoreline Court, Ste. 200
South San Francisco, CA 94080, USA
ACT20131018


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Sublingual therapy arriving for grass allergy

BY BRUCE JANCIN
Frontline Medical News

KEYSTONE, COLO. – Sublingual immunotherapy is finally coming.

Allergy therapy using rapidly dissolving oral tablets instead of subcutaneous injections has been approved in Europe for years. With Food and Drug Administration approval of sublingual immunotherapy tablets for the treatment of grass and ragweed allergies considered highly likely later this spring, the expectation is that patients, their referring physicians, and allergists will have many questions about this game-changing therapeutic innovation.

Dr. Harold S. Nelson, who closely follows developments in the field, provided answers and analysis at a meeting on allergy and respiratory diseases sponsored by National Jewish Health.

Among his key points:

- The effectiveness of sublingual immunotherapy (SLIT) for allergic rhinitis and allergic asthma is now thoroughly established. So are the optimal dosing regimens: SLIT tablets are dosed once daily at 30 times the optimal subcutaneous immunotherapy (SCIT) once-monthly maintenance dose. In other words, over the course of a month, a patient on SLIT will take a roughly 30 times greater dose of grass or ragweed allergen than will a patient on SCIT.
- SLIT, like conventional subcutaneous immunotherapy, is disease-modifying therapy, which prevents new sensitization and progression to asthma.
- SLIT for grass allergy will be approved for patients aged 5-65, while SLIT for ragweed will receive an indication for 18- to 65-year-olds.
- The optimal duration of SLIT is 3-4 years, which typically produces 7-8 years of persisting benefit before re-treatment is needed.
- SCIT results in faster clinical improvement than does SLIT. And at least through the first 12-15 months, SCIT also appears to be significantly more effective.
- The big advantages SLIT offers over SCIT are convenience and safety. Although in U.S. clinical trials 1 in 200-300 SLIT-treated patients experienced mild systemic reactions—typically with the first dose—no fatal or near-fatal anaphylactic reactions have occurred. That’s why SLIT will be approved for at-home use after a first in-office observed dose. However, the FDA will mandate that SLIT prescriptions be accompanied by co-prescription of an epinephrine auto-injector, according to Dr. Nelson of National Jewish Health in Denver and professor of medicine at the University of Colorado at Denver.

Once SLIT products win FDA approval, the therapy will get a CPT code and become, for the first time, a billable treatment – a most welcome development. But Dr. Nelson emphasized that SLIT’s approval will also create a new dilemma for physicians and their many patients with multiple allergies, say, to trees, dogs, and molds in addition to grass or ragweed.

“Most of the companies have no plans to take SLIT beyond the standardized extracts, which means grass, ragweed, house dust mite, and cat. … And it seems unlikely that anyone is going to put a patient on tablets and injections at the same time. So it’s a decision that will have to be made for every patient: whether the ability to treat grass and ragweed, and later, house dust mite and cat, is sufficient for that patient. Because if it’s not, then probably the patient is still a candidate for SCIT,” Dr. Nelson said.

The strategy of the companies developing SLIT is not that oral therapy is supposed to be a replacement for SCIT, but rather that it provides an immunotherapy option for patients who currently don’t receive it because they balk at the inconvenience of monthly in-office injections, he continued.

“The idea is that if these people are told, ‘You can just take a tablet at home,’ they’ll opt to get at least their allergies to grass and ragweed treated,” Dr. Nelson explained.

In a soon-to-be-published report, Dr. Nelson has reviewed 11 randomly...
The effectiveness of sublingual immunotherapy for allergic asthma is now thoroughly established.

DR. NELSON

mmonologically, compared with the no-treatment controls, with the benefits becoming significant in the first 1-3 months. However, the improvements in IgG4, IgE-blocking factor, facilitated antigen presentation, and the basal activation test were generally twice as great in the SCIT group. Moreover, the symptomatic response to nasal challenge—the only measure of clinical response utilized in the study—was significantly better than in controls only with SCIT (Clin. Exp. Allergy 2014;44:417-28).

“This is the best comparative study we have, and it may be the best we’ll get. Here both treatments are being given optimally, and it’s very clear that at least in the first year, SCIT beats SLIT. It looks as though SLIT is trying to catch up late but doesn’t quite get there through 15 months,” Dr. Nelson said.

Of note, an analysis of seven phase III clinical trials totaling nearly 2,700 adults and children showed that roughly half of them experienced transient local adverse reactions to grass SLIT.

Grass allergies are the most common seasonal allergies in the United States. The three standardized SLIT products under FDA review, all of which have been approved in Europe for years, are Grastek, a Timothy grass extract; Ragwitek; and Oralair, a five-grass product developed by the French company Stallergenes. Oralair, to be marketed in the United States by Greer, contains Timothy grass allergen as well as extracts of four other temperate pasture grasses. Of note, Bermuda and Bahia grasses, common causes of seasonal allergy, aren’t included in Oralair or Grastek.

The companies have pursued different dosing strategies. ALK recommends taking Grastek continuously year-round. Stallergenes recommends starting Oralair a few months before the start of grass allergy season and stopping when the pollen season is over (J. Allergy Clin. Immunol. 2011;128:559-66).

Dr. Nelson’s prediction that these three SLIT products are headed for FDA approval this spring stems from enthusiastic endorsements by the agency’s Allergenic Products Advisory Committee. The SLIT grass allergy products were recommended unanimously, and the ragweed SLIT also received a strongly favorable vote.

He reported serving as a consultant to Merck, Pearl Therapeutic, and Cir-cassia.

bjancin@frontlinemedcom.com
Advanced clinical providers proving their mettle

BY PATRICE WENDLING

NAPLES, Fla. – Complication rates are similar for advanced clinical practitioners and resident physicians performing key routine procedures in the ICU or trauma setting, a retrospective study found.

Advanced clinical practitioners (ACPs) performed 55,956 procedures with 11 complications (2%), while resident physicians (RPs) performed 1,020 procedures with 20 complications (2%).

Procedures consisted of arterial lines, central venous lines, bronchovascular lavage, thoracotomy tubes, percutaneous endoscopic gas-trotomy (PEG), and tracheostomies, Massanu Sirleaf, a board-certified acute care nurse practitioner, said at the annual scientific assembly of the Eastern Association for the Surgery of Trauma.

Major finding: The complication rate was 2% for advanced clinical providers (11/5,555) and resident physicians (210,020).

Data source: A retrospective study of 1,575 invasive procedures.

Disclosures: Ms. Sirleaf and her coauthors reported having no financial disclosures.

No differences were observed between the ACP and RP groups in mean ICU length of stay (3.7 vs. 3.9 days) or hospital stay (13.3 vs. 12.2 days).

Mortality rates were also similar for ACPs and RPs (9.7% vs. 9.7%; P = .07), despite significantly higher age (mean 54.5 years vs. 49.9 years) and APACHE II scores for the ACP group (mean 47.7 vs. 40.8).

“Our results demonstrate that ACPs have become a very important part of our health care team and substantially the safety of ACPs in performing surgical procedures in critically ill patients,” Ms. Sirleaf said.

Restrictions in resident work hours have imposed workload challenges on trauma centers, leading some to recruit nurse practitioners and physi-cian assistants to care for critically ill patients in the ICU and to perform invasive procedures that are previously done exclusively by physicians, she observed.

Very few studies, however, have addressed ACPs’ procedural competence and complication rates.

The retrospective study included all procedures performed from January to December 2011 in the trauma and surgical ICUs at the FH. ‘Sammie’ Ross Jr. Trauma Center, Carolina Medical Center.

Continued on following page.

Major findings:
- Advanced clinical providers (ACPs) and resident physicians (RPs) had similar complication rates in performing key routine procedures in the ICU or trauma setting.
- The complication rates were 2% for ACPs and 2% for RPs, with no significant differences observed in mortality rates and hospital lengths of stay.
- The study utilized a retrospective analysis of 1,575 invasive procedures performed by ACPs and RPs over a year.
- No differences were observed in ICU and hospital lengths of stay between the ACP and RP groups.
- Mortality rates were also similar for ACPs and RPs (9.7% vs. 9.7%; P = .07).
- The results suggest that ACPs have become a significant part of the health care team in trauma centers.

Disclosures:
- Massanu Sirleaf, a board-certified acute care nurse practitioner, reported no financial disclosures.
- The study was supported by unrestricted educational grants from Boehringer Ingelheim Institutional. Copyright 2013 Boehringer Ingelheim Institutional GmbH.

No further details were provided.
Center in Charlotte, N.C. Eight ACPs performed invasive procedures for surgical critical care patients under attending supervision, while three postgraduate year two (PGY2) surgical and emergency residents performed procedures for trauma patients.

Invited discussant Dr. Jeffrey Claridge, director of trauma, critical care, and burns at MetroHealth Medical Center in Cleveland, agreed with the study’s conclusion that complications were similar between ACPs and RPs, but went on to say that 2% is extremely low and that “something is missing or oversimplified.”

In particular, he pressed Ms. Sirleaf on where the procedures were performed, the level of supervision provided to ACPs, and how extensive the review of complications was other than procedural notes. For example, did the authors look at whether chest tubes fell out within 24 hours because they were inappropriately secured, PEG or trachecostomy sites that got infected, or breaks occurred in sterile technique.

Ms. Sirleaf replied that in addition to reviewing postprocedural notes, radiologists looked for complications 24 hours after chest tube placement and patients with a trachecostomy were followed for complications for 7 days by the attending.

Urgency of the procedure was not evaluated since the procedures were elective and most were performed at the bedside.

Work-hour restrictions have led some centers to recruit NPs and PAs to care for critically ill patients.

MS. SIRLEAF

“For the ACPs with a level of competency, just like interns at the beginning, they assisted the attending and as they got better, the majority of the procedure was performed by the ACP at the bedside with the attending scrubbed in,” she said.

At the time of the study, three ACPs had 1 year of experience, with up to 7 years’ experience in the remaining ACPs. Senior ACPs provided training along with the attendings, and both ACPs and RPs underwent quarterly simulation lab training on procedures. To maintain competency, Carolinas Medical Center also requires ACPs perform a set number of each type of procedure on a yearly basis and have these procedures witnessed and signed off on by an attending, said Ms. Sirleaf, now with Sharp Memorial Hospital, San Diego.

pwendling@frontlinemedcom.com

Aldosterone agonists central in HF

Guidelines from page 1

— in terms of benefits (see chart). “These data are quite striking,” Dr. Clyde W. Yancy observed in presenting highlights of the 2013 ACC/AHA guidelines at the Annual Cardiovascular Conference at Snowmass.

“For many years, we’ve functioned in a space where we thought there’s not that much we can do for heart failure, and I would now argue strenuously against that. You can see the incredibly low numbers needed to treat here. Only a handful of patients need to be exposed to these therapies to derive a significant benefit on mortality.”

‘Only a handful of patients need to be exposed to these therapies to derive a significant benefit on mortality.’

DR. YANCY

failure, and I would now argue strenuously against that. You can see the incredibly low numbers needed to treat here. Only a handful of patients need to be exposed to these therapies to derive a significant benefit on mortality. These are data we should incorporate in our clinical practice without exclusion,” declared Dr. Yancy, who chaired the heart failure guideline-writing committee.

The important caveat regarding the aldosterone antagonists is that they should be used only in patients with an estimated glomerular filtration rate greater than 30 mL/min per 1.73 m² and a serum potassium level below 5.0 mEq/dL. Otherwise that Class I/A recommendation plummets to III/B, meaning the treatment is inappropriate and potentially harmful, continued Dr. Yancy, professor of medicine and of medical social sciences and chief of cardiology at Northwestern University, Chicago.

The guidelines emphasize the imperative to implement what has come to be termed guideline-directed medical therapy, known by the abbreviation GDMT. The panel found persuasive an analysis showing that heart failure patients with reduced ejection fraction who were on two of seven evidence-based, guideline-directed management interventions had an adjusted 38% reduction in 2-year mortality risk compared with those on none or one, while those on three interventions had a 62% decrease in the odds of mortality and patients on four or more had mortality reductions of about 70% (J. Am. Heart Assoc. 2012;1:16-26).

The seven interventions are beta-blockers, ACE inhibitors or ARBs, aldosterone antagonists, anticoagulation for atrial fibrillation, cardiac resynchronization therapy, implantable cardioverter-defibrillators, and heart failure education for eligible patients. The guidelines advise strongly against the combined use of an ACE inhibitor and ARB. It’s an either/or treatment strategy. Studies indicate there is no additive benefit with the combination, only an increased risk of side effects.

An important innovation in the guidelines is the new prominence afforded to heart failure with preserved ejection fraction, known as HFpEF (pronounced hef-pef).

“What’s most different in the new heart failure guidelines is that we have uploaded HFpEF to the front page,” said Dr. Yancy. “We want you to appreciate how important it is. We recognize that there’s no evidence-based intervention that changes its natural history; rather, the focus is on identification and treatment of the comorbidities. It’s important to emphasize that this is a novel way of thinking about heart failure for a very important iteration of that disease.”

Among the other highlights of the guidelines is a clarification of the current role for biomarker-guided heart failure therapy. B-type natriuretic peptide (BNP) or N-terminal proBNP measurements are deemed useful in making the diagnosis of heart failure as well as in establishing prognosis.

Serial measurements can be used to titrate GDMT to optimal doses. But there are as yet no data to show that using the biomarkers to titrate GDMT to higher doses improves mortality.

The 2013 ACC/AHA Guideline for the Management of Heart Failure was developed in collaboration with the American Academy of Family Physicians, the American College of Chest Physicians, the Heart Rhythm Society, and the International Society for Heart and Lung Transplantation (J. Am. Coll. Cardiol. 2013;62:e147-239).

Dr. Yancy reported having no financial conflicts.

bjancin@frontlinemedcom.com

 Benefits of guideline-directed medical therapy for heart failure

<table>
<thead>
<tr>
<th>Drug</th>
<th>Relative risk reduction in mortality</th>
<th>Number needed to treat to prevent one death in 36 months</th>
<th>Relative risk reduction for heart failure hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydralazine/isosorbide dinitrate</td>
<td>43%</td>
<td>7</td>
<td>33%</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>34%</td>
<td>9</td>
<td>41%</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>30%</td>
<td>6</td>
<td>35%</td>
</tr>
<tr>
<td>ACE inhibitor or angiotensin receptor blocker</td>
<td>17%</td>
<td>26</td>
<td>31%</td>
</tr>
</tbody>
</table>

Source: Dr. Yancy

’...what’s most different in the new heart failure guidelines is that we have uploaded HFpEF to the front page,” said Dr. Yancy. “We want you to appreciate how important it is. We recognize that there’s no evidence-based intervention that changes its natural history; rather, the focus is on identification and treatment of the comorbidities. It’s important to emphasize that this is a novel way of thinking about heart failure for a very important iteration of that disease.”

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Dr. Yancy reported having no financial conflicts.

bjancin@frontlinemedcom.com

Dr. Jun Chiong, FCCP, comments: The new 2013 ACCF/AHA Guideline for the Management of Heart Failure provides a fresh and comprehensive guide to evaluation and management of heart failure patients.

The guideline has new areas that are going to be quite helpful for the providers. The indications for aldosterone antagonists are broadened for symptomatic HFpEF patients NYHA class II, III, and IV patients. Creatinine values needed to be = 2.5 mg/dL in men or = 2.0 mg/dL in women, and potassium =5.0 mEq/L are highlighted along with the necessity for careful monitoring of potassium, renal function, and diuretic dosing at initiation follow-up. Routine combined use of an ACE inhibitor, ARB, and aldosterone antagonist is considered potentially harmful and is not recommended.

bchiong@frontlinemedcom.com

VIEW ON THE NEWS
Palliative skills critical to ICU care

BY LEIGH FREDHOLM, M.D., AND STEPHEN BEKANICH, M.D.

Recently, members of our palliative care team participated in the care of a man approaching the end of his life. The patient had suffered an in-hospital cardiac arrest 4 weeks earlier, and though he had survived the immediate event, it resulted in anoxic encephalopathy, which rendered him incapable of making decisions.

When it became clear that the patient was declining despite full support, the hospital’s ethics committee was convened to determine goals of care and next steps, as the patient had no family or surrogate decision maker. After determination that the hospital staff had exercised due diligence in attempting to locate a surrogate, the physicians involved reviewed the patient’s case and recommended a change in goals to comfort care. More than one member of the committee expressed confusion as to what interventions are and are not included in comfort care, including medically administered nutrition and hydration (MANH).

Comfort care has traditionally included medications for distressing symptoms (pain, dyspnea, nausea), personal care for hygiene, and choice of place of death (home, hospital, nursing facility), usually with the assistance of a hospice agency.

As the number and complexity of interventions used near the end of life expand, clinicians and hospital staff report confusion about whether these interventions, generally considered to be life-sustaining treatments, can also be considered comfort care. We generally find that when interventions are considered in the context of the patient’s goals of care, the dilemma is clarified. Often the situation is made more complicated by considering the interventions before settling on goals. Broadly speaking, goals of care are derived from a careful consideration (by patient, physician, and family) of the natural history of the illness, expected course and prognosis, and patient preferences.

In the case of the above-referenced patient, we were unable to ascertained his goals because of neurological impairment. We did know, however, that the patient had steadfastly avoided hospitals and medical care of any kind. The attending hospitalist, pulmonologist, and palliative care physician agreed that the patient’s clinical status was declining despite all available interventions, and that his constellation of medical problems constituted a terminal condition. The physicians agreed that future ICU admission, resuscitation, and other new interventions would only prolong his dying process, but not permit him to live outside the hospital. At that time, the patient was receiving nutrition and hydration via a Dobhoff tube, and was tolerating enteral nutrition without excessive residuals or pulmonary secretions.

As with other interventions, *Continued on following page*
Continued from previous page

whether or not to consider MANH a part of comfort care is individualized. In this patient’s case, in the absence of evidence that he would not want MANH, it was continued. Other patients have expressed the wish that they would under no circumstances accept MANH while receiving comfort care. Both are correct as long as they reflect that patient’s wishes.

With respect to other interventions—including but not limited to BiPAP, inotrope infusion, chemotherapy, radiation therapy, and transfusions—whether or not they provide comfort is a decision to be made jointly by the patient and physician(s). As advances in medicine allow patients to live longer with serious illness, the definition of comfort care must also expand.

Dr. Fredholm and Dr. Beckanich are codirectors of Seton Palliative Care, part of the University of Texas Southwestern Residency Programs in Austin.

“Palliatively Speaking,” appears monthly at chaplainstimelssnews.com.

# View on the News

Dr. Steven Q. Simpson, FCCP: Dr. Fredholm and Dr. Beckanich adeptly discuss how to weigh possible life-sustaining measures in terms of whether they are providing comfort for patients and how to ensure that such treatments are discussed with patients in that context. Additionally, they provide a very nice example of how to proceed when patients cannot communicate for themselves and have no family or other surrogates to speak for them. Join us in the Critical Care NetWork’s eCommunity.

# Relatively few in ICUs get end-of-life dialogue training

**By Sherry Boschert**

*Frontline Medical News*

SAN FRANCISCO – Despite training recommendations, half of physicians and less than a third of nurses surveyed in adult intensive care units at 56 California hospitals reported receiving formal training in talking with patients and families about the end of life.

A 2008 consensus statement by the American College of Critical Care Medicine included a recommendation for end-of-life communication skills training for clinicians to improve the care of patients dying in ICUs (Crit. Care Med. 2008;36:953-63).

Dr. Matthew H.R. Anstey and his associates approached 149 California hospitals to gauge the extent of implementation of this recommendation. At 56 hospitals, doctors and nurses who work in adult ICUs voluntarily completed an anonymous web-based survey. Eighty-four percent of the 1,363 respondents were nurses, he reported in a poster presentation at the Critical Care Congress, sponsored by the Society for Critical Care Medicine.

Overall, 32% of the respondents said they had received formal training in communication skills. A significantly higher percentage of doctors had undergone training (50%) compared with nurses (29%), said Dr. Anstey, who is currently a Resident in Internal Medicine at Kaiser Permanente in California.

Continued on following page

# Education Calendar

**CHEST 2014 Education Calendar**

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<tr>
<th>AIRWAY MANAGEMENT</th>
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<tr>
<td>Essentials of Airway Management: Skills, Planning, and Teamwork May 7</td>
<td>Essentials of Bronchoscopy June 6-7</td>
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<tr>
<td>Difficult Airway Management 2014 Update for the Practicing Intensivist May 8-10</td>
<td>Endobronchial Ultrasound June 1-2</td>
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<td>PAPNE=102</td>
<td>September 16-17</td>
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<tr>
<td>Peripheral Bronchoscopy June 22</td>
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<td>NEW! Comprehensive Pleural Procedures June 20-21</td>
<td>MECHANICAL VENTILATION</td>
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<td>NEW! Therapeutic Bronchoscopy in</td>
<td>Essentials of Mechanical Ventilation for Providers April 24</td>
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<td>NEW! Bronchoscopy in</td>
<td>Critical Care Medicine April 25-27</td>
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<tr>
<td>NEW! Essentials of Sleep-Disordered</td>
<td>Management July 25-27</td>
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<tr>
<td>Breathing July 18</td>
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<tr>
<td>NEW! Management of Sleep-Disordered</td>
<td>Critical Care: Echocardiography May 3-4</td>
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<tr>
<td>Breathing July 19-20</td>
<td>September 21-27</td>
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**CHEST 2014 October 25-30**

**PULMONOLOGY**

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<th>ULTRASONOGRAPHY</th>
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<td>Ultrasonography: Essentials in Critical Care April 1-2</td>
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<tr>
<td>Critical Care</td>
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<tr>
<td>Thoracic and Vascular Ultrasound May 1-2</td>
</tr>
<tr>
<td>Critical Care: Echocardiography May 3-4</td>
</tr>
<tr>
<td>September 18-19</td>
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</tbody>
</table>

**CHEST 2014 Advanced Critical Care Echocardiography May 29-31 | chestnet.org/live-learning**
Palliative care shortens ICU, hospital stays, review shows

BY SHERRY BOSCHERT
Frontline Medical News

SAN FRANCISCO – Palliative care in the intensive care unit reduces the length of stay in the ICU and the hospital without changing mortality rates or family satisfaction, according to a review of the literature.

Although measurements of family satisfaction overall didn’t change much from palliative care of a loved one in the ICU, some measures of components of satisfaction increased with palliative care, such as improved communication with the physician, better consensus around the goals of care, and decreased anxiety and depression in family members, reported Dr. Rebecca A. Aslakson of Johns Hopkins University, Baltimore, and her colleagues.

Dr. Aslakson presented the findings at the Critical Care Congress, sponsored by the Society for Critical Care Medicine.

Dr. Aslakson and her associates were unable to perform a formal meta-analysis of the 37 published trials of palliative care in the ICU because of the heterogeneity of the studies, which looked at more than 40 different outcomes.

Instead, their systematic review grouped results under four outcomes that commonly were measured, and assessed those either by the number of studies or by the number of patients studied.

ICU length of stay decreased with palliative care in 13 of 21 studies (62%) that used this outcome and in 59% of 9,368 patients in those studies. Mortality decreased in one small study (6%) and in one larger study (6%).

“Talking about big-picture issues and goals of care doesn’t lead to people dying,” Dr. Aslakson said. “No harm came in any of these studies.” Some separate studies of palliative care outside of ICUs reported that this increases hope, “because people feel that they have more control over their choices and what’s happening to their loved ones,” she added.

**Integrative vs. consultative model**

Dr. Aslakson and her associates also reviewed studies based on whether the interventions used integrative or consultative models of palliative care.

Generally, consultative models bring outsiders into the ICU to help provide palliative care, and integrative models train the ICU team to be the palliative care providers. In reality, the two models may overlap. For this review, the investigators applied mutually exclusive definitions to 36 of the studies.

In 18 studies of integrative interventions, members of the ICU team were the only caregivers in face-to-face interactions with the patient and families. In 18 studies of consultative interventions, palliative care providers included others besides the ICU team.

In the studies of integrative palliative care, ICU length of stay decreased with palliative care in four of nine studies (44%) that measured this outcome and in 52% of 6,963 patients in those studies, she reported. Hospital length of stay decreased in two of five studies (40%) and in 24% of 3,812 patients. Family satisfaction changed in none of 15 studies, and mortality decreased in 1 of 5 studies (20%) and in 34% of 3,807 patients.

In the studies of consultative care, ICU length of stay decreased with palliative care in 9 of 12 studies (75%) that measured this outcome and in 79% of 2,405 patients in those studies. Hospital length of stay decreased in six of nine studies (67%) and in 79% of 2,005 patients. Family satisfaction increased in one of four studies (25%) and in 21% of 429 patients. Mortality increased in 1 of 11 studies (9%) and in 5% of 2,162 patients.

One model isn’t necessarily better than the other, Dr. Aslakson said. Integrative palliative care may work best in a closed ICU with perhaps four or five intensivists in a relatively small unit. An integrative approach can be much more difficult in open or semiopen ICUs that have “40 different doctors floating around,” she said. “We tried that in my unit, and it didn’t work that well.”

Continued on following page

**VIEW ON THE NEWS**

Dr. Jennifer Cox, FCCP, comments: Dr. Aslakson and colleagues’ systematic review adds to the body of literature that demonstrates no mortality increase when palliative care measures are initiated in the ICU. Shorter lengths of stay both in the ICU and hospital were other positive outcomes noted without a significant change in patient or family satisfaction. These findings were independent of whether an integrative or consultative approach to palliative care was undertaken. This should encourage physicians to examine their practice setting and determine which approach meets the needs of their ICU and begin to utilize palliative care earlier and more aggressively without fear of increasing mortality.
Continued from previous page

Different ICUs need palliative care models that fit them. “Look at your unit, the way it works, and who the providers are, then look at the literature and see what matches that and what might work for your unit,” she said.

Outcomes of better communication
A previous, separate review of the medical literature identified 21 controlled trials of 16 interventions to improve communication in ICUs between families and care providers. Overall, the interventions improved emotional outcomes for families and reduced ICU length of stay and treatment intensity (Chest 2011;139:543-554), she noted.

Yet another prior review of the literature reported that interventions to promote family meetings, use empathetic communication skills, and employ palliative care consultations improved family satisfaction and reduced ICU length of stay and the adverse effects of family bereavement (Curr. Opin. Crit. Care 2009;15:569-77). Dr. Aslakson reported having no financial disclosures.

Adempas (riociguat) tablets, for oral use
Initial U.S. Approval: 2013

BRIEF SUMMARY of prescribing information

Do not administer Adempas to patients with CFH because it may cause fetal harm (see Contraindications (4) and Use in Specific Populations (8.1)).

1. INDICATIONS AND USAGE

1.1 Chronic-Thromboembolic Pulmonary Hypertension
Adempas is indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (WHO Group 4) after surgical treatment, or inoperable (CTEPH), to improve exercise capacity and WHO functional class [see Clinical Studies (14.1)].

1.2 Pulmonary Arterial Hypertension
Adempas is indicated for the treatment of adults with pulmonary arterial hypertension (PAH), (WHO Group 1), to improve exercise capacity, WHO functional class and to delay clinical worsening.

Efficacy was shown in patients on Adempas monotherapy or in combination with endothelin receptor antagonists or prostanoids. Studies establishing effectiveness included predominately patients with WHO functional class II–III and etiologies of idiopathic or heritable PAH (6%) or PAH associated with connective tissue diseases (25%) [see Clinical Studies (14.2)].

4 CONTRAINDICATIONS

4.1 Pregnancy
Adempas may cause fetal harm when administered to a pregnant woman. Adempas is contraindicated in females who are pregnant. Adempas was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant during treatment, monthly during treatment, and 1 month after stopping treatment.

Females can only receive Adempas through the Adempas REMS Program, a restricted distribution program [see Warnings and Precautions (5.1), Use in Specific Populations (8.1), 8.6 and Dosage and Administration (2.3), Warnings and Precautions (5.2) and Use in Specific Populations (8.1, 8.6)].

5.5 Pulmonary Veno-Occlusive Disease
Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Therefore, administration of Adempas to such patients is not recommended. Should signs of pulmonary edema occur, the possibility of associated PVOD should be considered and, if confirmed, discontinue treatment with Adempas.

5.4 Bleeding
In the placebo-controlled clinical trials program, serious bleeding occurred in 2.4% of patients taking Adempas compared to 0% of placebo patients. Serious hemoptysis occurred in 5 (1%) patients taking Adempas compared to 0 placebo patients, including one event with fatal outcome. Serious hemorrhagic events also included 2 patients with vaginal hemorrhage, 2 with calf/tether site hemorrhage, and 1 each with subdural hematoma, hematemesis, and intra-abdominal hemorrhage.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Embryo-Fetal Toxicity [see Warnings and Precautions (5.1)]
- Hypotension [see Warnings and Precautions (5.3)]
- Bleeding [see Warnings and Precautions (5.4)]

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 to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflect exposure to Adempas in two, randomized, double blind, placebo-controlled trials in patients with inoperable or recurrent/persistent CTEPH (CHEST-1) and treatment naive or pre-treated PAH patients (PATENT-1). The population [Adempas: n = 490; Placebo: n = 214] was between the age of 18 and 80 years [see Clinical Studies (14.1, 14.2)].

The safety profile of Adempas in patients with inoperable or recurrent/ persistent CTEPH (CHEST-1) and treatment naive or pre-treated PAH (PATENT-1) were similar. Therefore, adverse drug reactions (ADRs) identified from the 12 and 16 week placebo-controlled trials for PAH and CTEPH respectively were pooled, and those occurring more frequently on Adempas than placebo (≥3%) are displayed in Table 1 below. Most adverse events in Table 1 can be ascribed to the vasodilatory mechanism of action of Adempas.

The overall rates of discontinuation due to an adverse event in the pivotal placebo-controlled trials were 2.9% for Adempas and 5.1% for placebo (pooled data).

Table 1: Adverse Reactions Occurring More Frequently (≥3%) on Adempas than Placebo

<table>
<thead>
<tr>
<th>Table 1: Adverse Reactions Occurring More Frequently (≥3%) on Adempas than Placebo</th>
<th>Placebo % (n=214)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>27</td>
</tr>
<tr>
<td>Diarrhea and Gastritis</td>
<td>23</td>
</tr>
<tr>
<td>Dizziness</td>
<td>29</td>
</tr>
<tr>
<td>Nausea</td>
<td>14</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10</td>
</tr>
<tr>
<td>Anemia (including laboratory parameters)</td>
<td>7</td>
</tr>
<tr>
<td>Gastrouresophageal reflux disease</td>
<td>5</td>
</tr>
<tr>
<td>Constipation</td>
<td>5</td>
</tr>
</tbody>
</table>

Other events that were seen more frequently in riociguat compared to placebo and potentially related to treatment were: palpitations, nasal congestion, epistaxis, dyspnea, abdominal distension and peripheral edema. With longer observation in uncontrolled long-term extension studies the safety profile was similar to that observed in the placebo controlled phase 3 trials.

7 DRUG INTERACTIONS

7.2 Pharmacodynamic Interactions with Adempas
Nitrates: Co-administration of Adempas with nitrates (such as isosorbide dinitrate) or PDE Inhibitors: Co-administration of Adempas with phosphodiesterase (PDE) inhibitors (such as sildenafil, tadalafil, or vardenafil) or non-specific PDE inhibitors (such as dipyridamole or theophylline) is contraindicated because of hypotension [see Contraindications (4.3), Clinical Pharmacology (12.2)].

7.3 Pharmacokinetic Interactions with Adempas
Smoking: Plasma concentrations in smokers are reduced by 50-60% compared to nonsmokers. Based on pharmacokinetic modeling, for patients
Low vitamin D – poor ICU outcomes

Outcomes from page 1

a significant predictor of 30- and 90-day all-cause mortality in critically ill patients, even after adjustment for such factors as age, Charlson/Deyo index, sepsis, and season [Crit. Care Med. 2012;40:63-72]. It has also been shown to significantly predict acute kidney injury in the critically ill [Crit. Care Med. 2012;40:378-9]. For the current analysis, vitamin D levels were drawn upon ICU admission, at 72 hours, and every 7 days until hospital discharge in 200 of 234 consecutive adult trauma patients admitted to the ICU at the Level 1 Orlando Regional Medical Center during a 4-month period. Deficiency was defined as 25-hydroxyvitamin D of 20 ng/mL or less. All patients received nutritional support using a standard protocol, but not vitamin D supplementation.

Median vitamin D ICU admission levels in the 31 vitamin D-deficient patients were significantly lower than for nondeficient patients (16 ng/mL vs. 28 ng/mL; P less than .001). Levels decreased a median of 4 ng/mL at 72 hours in both groups, but only the sufficient group returned to admission baseline levels at week 2, reported Dr. Ibrahim, a critical care surgeon with the medical center.

This demonstrates that if we wish to obtain normal vitamin D levels in these patients, we will have to supplement them with much higher doses than are provided in enteral formulas,” he said in an interview.

Patients with vitamin D deficiency spent more time than did nondeficient patients in the ICU (median 3 days vs. 2.7 days) and hospital (median 8.4 days vs. 7.1 days), but these trends did not reach statistical significance.

Significantly more deficient patients, however, remained in the hospital for at least 2 weeks (37% vs. 20%). The investigators were unable to show a difference in mortality between the deficient and nondeficient patients.

We have to supplement patients with much higher doses than are provided in enteral formulas.

DR. IBRAHIM

We have to supplement patients with much higher doses than are provided in enteral formulas.

DR. IBRAHIM

“...
Continued from previous page

groups (16% vs. 12%; \( P = .51 \)), possibly because the study was underpowered, he said.

Deficient and sufficient patients did not differ in age (median 48 years vs. 44 years), body mass index (26.2 kg/m² vs. 25.7 kg/m²), admission ionized calcium (1.06 mmol/L for both), or Injury Severity Score (14 vs. 13). Only APACHE II scores were significantly higher in deficient patients (20 vs. 15).

“It makes sense that with the significant difference in APACHE II score, one would expect to see a similar difference in mortality, but again we were unable to show this with this study,” Dr. Ibrahim said.

Prehospital factors significantly associated with low vitamin D status were African American race, diabetes, and lack of vitamin D supplementation.

Vitamin D supplementation may be helpful in critically ill trauma patients during hospitalization, but more research is needed, Dr. Ibrahim said. The group is planning a supplementation study, looking at vitamin D dosing and frequency of testing.

“Our first goal was to demonstrate a significant incidence, which we did,” he said. “It should be noted that the incidence was in a location with probably one of the highest amounts of sunshine in the country and that the findings may underestimate what one would find in other areas of the United States.”

Dr. Oscar Guillamondegui, of Vanderbilt University Medical Center in Nashville, Tenn., who proctored the poster session, said he would expect vitamin D levels to be lower in acutely sick patients requiring ICU management because production of vitamin D–binding protein, a subprotein in the albumin family of proteins involved in vitamin D transport and storage, is decreased in high stress situations to allow for the increase in acute phase protein production.

“Although the data are intriguing, as a retrospective study, it is too early to suggest that supplementation is essential,” he said.

Dr. Ibrahim and Dr. Guillamondegui reported having no financial disclosures.

To determine epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) rearrangement status in the diagnosis of advanced non-small cell lung cancer (NSCLC),

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Another surgeon’s error – Must you tell the patient?

Patients have a right to honest information.

BY DR. SUSAN D. MOFFATT-BRUCE

S urgeons have a moral and ethical obligation to inform a patient when a medical error has occurred, including cases when the error was made by another surgeon.

Principles that support complete and honest disclosure to the patient and/or the patient’s family in such cases include professional obligation on the part of both the surgeon who made the error and the surgeon who discovered the error, the integrity of both surgeons, the patient’s right to informed care throughout the continuum of care, and the patient’s right to informed consent.

With respect to the first, the American Medical Association’s code of ethics provides a framework for disclosure; it clearly states that situations occur in which a patient experiences significant complications that may have resulted from a physician’s mistake or judgment and that the physician is ethically required to inform the patient of all facts necessary to ensure understanding of the error that occurred.

The American College of Physicians’ ethics manual also states that physicians should disclose to patients information about procedural or judgment errors made during the course of care, as long as that information is pertinent and material to the patient’s well-being.

Errors do not necessarily imply negligence or unethical behavior, but failure to disclose may.

As for patients’ rights, I think that patients are entitled to honest information. They should not bear the burden of determining how they came to be in another surgeon’s care.

Patients with complications may have impactful financial burdens that result from the additional treatment that is needed, and without all pertinent information, they may have difficulty understanding the benefits, such as deferment of payments, to which they are entitled.

The patient is entitled to informed consent, and this requires an understanding of the conditions under which they arrived in another surgeon’s care. If a second procedure is required, the patient must be made aware of potential complications – including how the effects of the initial error might impact outcomes.

Although surgeons have an ethical obligation to disclose errors made by another surgeon, this is admittedly a difficult task. Pressures from society and medical professionals can make disclosure difficult, but the benefits of disclosure are very real; studies show that open, honest communication improves patient satisfaction, strengthens the physician-patient relationship, and can ultimately improve outcomes.

Disclosure also has the potential to improve the well-being of the surgeons involved, through reliving feelings of guilt, and satisfying the need to fulfill one’s obligations. Furthermore, data suggest that error disclosure reduces long-term litigation and costs. Admittedly, however, there are few data on how disclosure of another surgeon’s errors might result in reduction of litigation and costs.

Ultimately, supporting a just culture allows us to emphasize the importance of disclosing errors and to be accountable in setting a standard that involves exploring errors rather than ignoring them; it must be remembered, though, that this process of disclosure involves obtaining facts to help both surgeons and patients understand what truly happened.

Surgeon-to-surgeon discussions can be productive and can facilitate disclosure. However, if the doctor who made the error declines to be part of the disclosure process, one still has an obligation to disclose the error and to answer the patient’s questions honestly.

This approach requires a commitment to support surgeons in their efforts to promote transparency, and it requires a clear understanding of our obligations and the role of disclosure during training; we need to engage medical students and residents in the very important role of health care advocacy.

Dr. Moffatt-Bruce is an associate professor of thoracic surgery at the Ohio State University, Columbus.

Discuss the error with the responsible physician.

BY DR. CHADDRICK E. DENLINGER

S urgeons do not have an obligation to disclose to a patient another surgeon’s possible medical error.

A consensus has been reached in medicine about our ethical duty to inform patients about our own medical errors. Although nondisclosure has previously been rationalized by concerns about invoking anxiety or confusion in the patient, this approach has largely been discredited; disclosure preserves patient trust and bolsters the physician-patient relationship.

However, it is an entirely different story when it comes to disclosing another surgeon’s mistake – a situation that is quite common. A recent survey showed that two-thirds of respondents had encountered a similar dilemma in the past 6 months (Qual. Saf. Health Care 2009;18:209-12).

The approach that physicians have previously taken when faced with this dilemma is an important measure of what they believe represents an ethical or just response. A poll of many of my colleagues across the country and at my own institution suggests that the preferred approach is to provide appropriate care for the patient and to answer their questions honestly, but to not proactively disclose the perceived medical error.

In fact, this was the preferred approach of every surgeon who responded.

A recent article in the New England Journal of Medicine addressed this very topic. The authors noted that there is little guidance available regarding the reporting of another physician’s error (2013;369:1752-7).

Among the challenges inherent in disclosing another’s mistake is the difficulty in determining exactly what happened. Uncertainty inevitably exists regarding the conversations that took place between the patient and the surgeon, and also about what actually defines a medical error. Incidents regarded as medical errors may comprise a large spectrum, ranging from “not what I would have done – but within the standard of care,” to “blatant negligence.”

Several studies suggest that highly trained physicians and surgeons routinely disagree about whether negligence has occurred in a given case. In one study, two reviewers disagreed 38% of the time as to whether appropriate care was provided.

Physicians have difficulty judging if the standard of care has been met. Therefore, it is not acceptable for each of us to assume we are the medical expert capable of rendering an opinion of whether previous care was appropriate and informing patients of our opinion.

Physicians overwhelmingly report that in the event they are responsible for a medical error discovered by another physician, they would prefer that the physician come to them first to discuss the matter. In fact, 93% of 400 respondents in one survey reported this preference.

The most acceptable approach when dealing with a peer’s medical error is to discuss the error with the responsible physician and to encourage the physician to disclose any error with the patient.

If there is disagreement as to whether an error occurred, institutional guidance should be applied. Only a collaborative approach can appropriately meet the needs of the patient and family after harmful medical errors.

Dr. Denlinger is an associate professor at the Medical University of South Carolina, Charleston.
Breath test could improve lung cancer screening

BY SHARON WORCESTER
Frontline Medical News

ORLANDO – The presence of certain carbonyl volatile organic compounds in exhaled breath can aid in the detection of early lung cancer, according to Dr. Michael Bousamra.

An analysis of volatile organic compounds (VOCs) in the exhaled breath of 10 lung cancer patients and 88 controls, including 45 who were smokers and 43 who were nonsmokers, identified four carbonyl VOCs that occurred significantly more often in the lung cancer patients’ breath samples than in the control samples: 2-butanone, 3-hydroxy-2-butanone, hydroxyacetaldehyde, and 4-hydroxyhexenal.

Further study of 151 patients with suspicious lung nodules found no single VOC marker that was independently predictive of lung cancer, but when the levels of three or more were elevated in a single patient, the sensitivity and specificity for lung cancer were 60% and 95.2%, respectively. When the levels of at least two of the VOCs were elevated, the sensitivity and specificity were 84.7% and 81%, respectively, and when at least one was elevated, the sensitivity and specificity were 93.8% and 45.2%, respectively.

The absence of VOC elevation was predictive of benign disease in 80% of cases, Dr. Bousamra of the University of Louisville, Ky., reported at the annual meeting of the Society of Thoracic Surgeons.

Notably, the concentrations of three of four VOCs in samples from lung cancer patients decreased to the level found in healthy controls after resection, he explained.

Continued on following page
The microchip used in the study detected four carbonyl volatile organic compounds that appeared more often in the breath samples of lung cancer patients.

IMPORTANT SAFETY INFORMATION ABOUT SYMBICORT (continued)

- SYMBICORT is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms
- SYMBICORT should not be initiated in patients during rapidly deteriorating episodes of asthma or COPD
- Patients who are receiving SYMBICORT should not use additional formoterol or other LABA for any reason
- Localized infections of the mouth and pharynx with Candida albicans has occurred in patients treated with SYMBICORT. Patients should rinse the mouth after inhalation of SYMBICORT
- Lower respiratory tract infections, including pneumonia, have been reported following the inhaled administration of corticosteroids
- Due to possible immunosuppression, potential worsening of infections could occur. A more serious or even fatal course of chickenpox or measles can occur in susceptible patients
- It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression may occur, particularly at higher doses. Particular care is needed for patients who are transferred from systemically active corticosteroids to inhaled corticosteroids. Deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids
- Caution should be exercised when considering administration of SYMBICORT in patients on long-term ketoconazole and other known potent CYP3A4 inhibitors
- As with other inhaled medications, paradoxical bronchospasm may occur with SYMBICORT
- Immediate hypersensitivity reactions may occur as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm
- Excessive beta-adrenergic stimulation has been associated with central nervous system and cardiovascular effects. SYMBICORT should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension
- Long-term use of orally inhaled corticosteroids may result in a decrease in bone mineral density (BMD). Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating SYMBICORT and periodically thereafter
- Glaucoma, increased intraocular pressure, and cataracts have been reported following the inhaled administration of corticosteroids, including budesonide, a component of SYMBICORT. Close monitoring is warranted in patients with a history of increased intraocular pressure, glaucoma, or cataracts
- In rare cases, patients on inhaled corticosteroids may present with systemic eosinophilic conditions
- SYMBICORT should be used with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines
- Beta-adrenergic agonist medications may produce hypokalemia and hyperglycemia in some patients
- The most common adverse reactions ≥3% reported in COPD clinical trials included nasopharyngitis, oral candidiasis, bronchitis, sinusitis, and upper respiratory tract infection
- SYMBICORT should be administered with caution to patients being treated with MAO inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents
- Beta-blockers may not only block the pulmonary effect of beta-agonists, such as formoterol, but may produce severe bronchospasm in patients with asthma
- ECG changes and/or hypokalemia associated with nonpotassium-sparing diuretics may worsen with concomitant beta-agonists. Use caution with the coadministration of SYMBICORT

For formulary information, please visit Symboic teaching Tools.com.

Please see Brief Summary of full Prescribing Information, including Boxed WARNING, on adjacent pages.

References:

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SYMBICORT® 80/4.5 (budesonide 80 mcg and formoterol fumarate dihydrate 4.5 mcg) Inhalation Aerosol

SYMBICORT® 160/4.5 (budesonide 160 mcg and formoterol fumarate dihydrate 4.5 mcg) Inhalation Aerosol

For Oral Inhalation Only

SYMBICORT® is contraindicated in the following conditions:

- Systemic corticosteroid use after transferring to systemic corticosteroids for treatment of asthma
- A 28-week, placebo-controlled US study comparing the safety of systemically administered corticosteroids, inhaled corticosteroids alone, and inhaled corticosteroids plus a long-acting beta-2-agonist (LABA) in patients with asthma, found no significant differences in serious adverse events between treatment groups.

The use of SYMBICORT® is contraindicated in the following conditions:

- Systemic corticosteroid use after transferring to systemic corticosteroids for treatment of asthma
- A 28-week, placebo-controlled US study comparing the safety of systemically administered corticosteroids, inhaled corticosteroids alone, and inhaled corticosteroids plus a long-acting beta-2-agonist (LABA) in patients with asthma, found no significant differences in serious adverse events between treatment groups.

When three or more carbonyl markers were present, the probability of cancer was very high; when no carbonyl markers – or even one – was elevated, associated pulmonary disease was likely benign.

In conclusion, SYMBICORT® is not recommended for use as a regular maintenance therapy, except in patients who are inadequately controlled with low or medium dose inhaled corticosteroids and whose disease severity clearly indicates the need for a LABA. A regular basis (e.g., 4 times a day) should be instructed with SYMBICORT® to achieve the lowest dose of LABA consistent with therapeutic response. When transferring to MTC+, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

Exposure to varicella vaccine was evaluated in pediatric patients with asthma ages 12 months to 8 years with budesonide inhalation suspension. In this controlled study, the development of localized infections of the mouth and pharynx with varicella infection in patients treated with MTC+ has been observed. When such infections are suspected, treatment should be discontinued. When transferring to MTC+, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. The sizes of these studies were not adequate to precisely quantify the serious asthma exacerbation rates between treatment groups.

Formoterol is a long-acting beta-2-agonist (LABA) and can be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract, extrapulmonary fungal, bacterial, viral, or parasitic infections, or ocular herpes simplex.

During periods of stress or a severe asthma attack, patients with asthma should be instructed to use their maximum recommended dose of LABA plus inhaled corticosteroid. However, for patients 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 affects the risk of developing a disseminated infection is not known. The contraindication of the underlying disease or prior corticosteroid therapy is not always known, especially in patients with a history of asthma.

The benefit of long-term low dose inhaled corticosteroids in reducing the frequency of exacerbations appears to be superior to other forms of treatment. Patients using SYMBICORT® should not use additional long-acting beta-2-agonists for any reason (see WARNINGS AND PRECAUTIONS).

Inhaled corticosteroids should be used with caution and close observation, in patients with chronic bronchitis, emphysema, or bronchiectasis. A 28-week, placebo-controlled US study comparing the safety of systemically administered corticosteroids, inhaled corticosteroids alone, and inhaled corticosteroids plus a long-acting beta-2-agonist (LABA) in patients with asthma, found no significant differences in serious adverse events between treatment groups.

The benefit of long-term low dose inhaled corticosteroids in reducing the frequency of exacerbations appears to be superior to other forms of treatment. Patients using SYMBICORT® should not use additional long-acting beta-2-agonists for any reason (see WARNINGS AND PRECAUTIONS).

The benefit of long-term low dose inhaled corticosteroids in reducing the frequency of exacerbations appears to be superior to other forms of treatment. Patients using SYMBICORT® should not use additional long-acting beta-2-agonists for any reason (see WARNINGS AND PRECAUTIONS).
The possibilities for this type of testing are exciting, and this work represents a window into the future of lung cancer screening and diagnosis.

Continued from previous page

Clinical Trials Experience in Asthma

Patients 12 years and older

The overall safety data in adults and adolescents is based on 15 active, and placebo-controlled clinical trials in which 2,032 patients ages 12 years and older (1,082 females and 951 males) with asthma of varying severity were treated with SYMBICORT 160/4.5 mcg for 1 to 52 weeks. In these trials, the patients on SYMBICORT had a mean age of 38 years and were predominantly Caucasian (83%). The incidence of serious adverse events in Table 1 below is based upon pooled data from 15 of these 15-week, double-blind, placebo-controlled clinical studies in which 401 adult and adolescent patients (165 females and 236 males) ages 12 years and older were treated with two inhalations of SYMBICORT 80/4.5 mcg or SYMBICORT 160/4.5 mcg twice daily. Taken individually, all adverse events that occurred at an incidence of 2 or more% on any one SYMBICORT group are more frequently than in the placebo group with twice daily dosing. In considering these data, the increased average duration of patient exposure for SYMBICORT patients should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

Table 1 Adverse reactions occurring at an incidence of 2% or more and commonly reported in placebo-group patients, pooled data from three 12-week, double-blind, placebo-controlled clinical trials in a 10 year old child.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>SYMBICORT 80/4.5 mcg</th>
<th>SYMBICORT 160/4.5 mcg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headaches</td>
<td>19.4%</td>
<td>17.4%</td>
<td>10.8%</td>
</tr>
<tr>
<td>Nausea</td>
<td>25.5%</td>
<td>22.2%</td>
<td>10.8%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8.2%</td>
<td>8.9%</td>
<td>4.0%</td>
</tr>
</tbody>
</table>

Your research has important implications for clinical practice and public health. By identifying potential areas for intervention, your study may help guide future research directions and improve patient outcomes.
the duration of lung cancer within 2 years. For this type of testing, the excitation is a window, and the work of Dr. Boussamara and his colleagues represents a window into the future of lung cancer screening and diagnosis, according to the esteemed dermatologist, Dr. Tom Varghese Jr., who is with the University of Washington in Seattle.

Lung cancer is the leading cause of cancer deaths worldwide, with higher mortality than the next three leading causes of cancer death combined, Dr. Varghese said.

A large screening trial showed that using low-dose CT for screening could reduce mortality by 20%—a finding that led to the recent endorsement by the U.S. Preventive Services Task Force of low-dose screening CTs for patients who are at high risk.

Such a screening program, if it were applied using strict criteria, "would avert 12,000 lung cancer deaths today," he asserted. Adding measurement of VOCS in exhaled breath to the screening protocol could result in fewer invasive procedures for abnormal screening results, and VOCS measurement could thus prove to be a simple, straightforward cost-saving measure, Dr. Varghese added.

**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). Budesonide is an inhibitor of CYP3A4, which can enhance the plasma concentration of orally administered budesonide. Concurrent administration of CYPRAS may inhibit the metabolism of, and increase the metabolites exposure to, budesonide. Caution should be exercised when considering the concomitant administration of SYMBICORT with long-term ketoconazole and other strong CYP3A4 inhibitors (eg, danazol, megestrol, mifepristone, nelfinavir, ritonavir, nevirapine, saquinavir, telithromycin) [see WARNINGS AND PRECAUTIONS].

**Membrane Oxidative Inhibitors and Interferon Antiproliferants**

SYMBICORT should be administered with caution to patients being treated with membrane oxide inhibitors or interferon antiproliferants, or within 2 weeks of discontinuing the use of aminoglutethimide. Caution should also be exercised when considering the concomitant administration of SYMBICORT with the systemic major inhibitor of CYP3A4, such as amlodipine, amiodarone, cyclosporine, diltiazem, ergot alkaloids (eg, methysergide), HIV protease inhibitors (eg, ritonavir), monoclonal antibodies (eg, infliximab), and thiazolidinediones [see WARNINGS AND PRECAUTIONS].

**Nociceptor Receptor Blocking Agents**

Beta-agonists (including e.g., isoprenaline) may not only block the pulmonary effect of beta-agonists, such as formoterol, but may produce systemic adverse effects. Formoterol was administered with caution.

**Drugs**

The ECG changes and/or hypokalaemia may result from the administration of non-steroidal anti-inflammatory drugs (such as ibuprofen) or, rarely, acebutolol, especially when the recommended dose of the beta-agonist is exceeded. Caution is advised in the concomitant administration of SYMBICORT with non-steroidal anti-inflammatory drugs.

**Pregnancy**

**Topical Effects**

**Prostaglandins C**

There are an adequate and well-controlled studies of SYMBICORT in pregnant women. SYMBICORT was teratogenic and embryocidal in rats. Budesonide was not significantly embryotoxic or teratogenic in rabbits, but in utero human embryonic and fetal death rates were not increased in women treated with a single 4 mg daily dose of budesonide. Formoterol fumarate was also embryotoxic, increased postimplantation deaths and decreased fetal weight in rats. Therefore, SYMBICORT should be used during pregnancy only if the potential benefit to the potential risk to the fetus justifies the potential risk to the mother.

**Sympathomimetic Amine Drugs**

Beta-blockers (including e.g., propranolol) and beta-adrenergic blocking agents in patients with asthma. In this setting, beta-adrenergic blockade could be contraindicated, unless this should be administered with caution.

**Diluents**

The EU changes and/or hypokalaemia may result from the administration of non-steroidal anti-inflammatory drugs (such as ibuprofen) or, rarely, acebutolol, especially when the recommended dose of the beta-agonist is exceeded. Caution is advised in the concomitant administration of SYMBICORT with non-steroidal anti-inflammatory drugs.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

In a study of 1447 asthmatic patients 6 to 12 years of age who also received SYMBICORT twice daily in studies of similar design, no adverse events occurred in the intercurrent illness were expected to be a simple, straightforward cost-saving measure, Dr. Varghese added. 16_21CH14_3.qxp  3/7/2014  3:15 PM  Page 21

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PRESIDENT’S REPORT: New Year’s resolution reboot?

BY DR. MICHAEL H. BAUMANN, FCCP

As I write this article, I am looking out a hotel window at a very cold Chicago landscape (I’m talking really cold for a guy from Mississippi). We just completed a very productive CHEST 2014 Executive Program Committee meeting to plan our annual program for this October in Austin, Texas. This effort was expertly led by Dr. Mark Metersky and his vice-chairs, Drs. Alex Niven and Jean Bourbeau, with great contributions by a superb group of executive committee members and the CHEST staff. We have an exciting program planned for you this year in Austin! The planning meeting was followed by the traditional “thank you” dinner for the planning committee participants. One of my New Year’s resolutions went flying out the window, yet again: eating sensibly! Hard for me to resist great food. I bet I’m not alone. I am more than 2 months into the yearly “resolution game.” Not one of my resolutions is intact – as usual. Like many of you, I bet, I set my sights a bit too high. My plans included eating more sensibly (not really that tough of a target, except cheese curls and French fries are irresistible), getting more regular exercise (my Nordic Track® often sits unused – yes, I’m that old – I actually own a Nordic Track), get home earlier each evening (there’s always something coming up at work), and not working as much on the weekends, or better yet, not at all (guess when I’m writing this).

Time for a resolution reboot! Yep, I “borrowed” that term from Headline News where I heard the phrase one early morning when the Nordic Track and I were getting reacquainted. I’d like to offer you several resolution ideas that should be easy to accomplish, and, yes, involve CHEST.

1. Come to CHEST World Congress in Madrid, March 21-24 (www.chestworldcongress2014.org/). I realize by the time this is published, time may be short. This is a fantastic program in collaboration with our partner, the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) and offers great and innovative content in a wonderful setting. Be sure to take advantage of the beautiful treasures of Madrid! One of those great treasures is the food! (There goes my resolution again.) Yes, this suggested CHEST resolution may be the hardest to accomplish, but the effort will be well rewarded.

2. Make your plans now to attend CHEST 2014 in Austin, Texas, (chestmeeting.chestnet.org). As noted, we just completed our program planning to include hands-on simulation, interactive sessions, and many more unique learning opportunities. Austin is a great city with much to offer, including world famous music, great barbecue, and other cuisine (food again – I better reboot that resolution, or just boot it).

3. Submit an abstract to CHEST 2014! This is a great way to show off the great care you have been providing for your patients!

4. Our new global headquarters opened in February. This fantastic facility offers an Innovation, Simulation, and Training Center that includes six simulation labs looking just like ICU rooms. Plan to attend one of our many new simulation offerings this year covering a myriad of topics, including ultrasound and mechanical ventilation. Look for even more exciting offerings over the year, as we take full advantage of this wonderful new resource, and sign up at (www.chestnet.org/Education/Products/Learning).

5. Join our e-Community or become even more active in the e-Community (www.chestnet.org/Networks/eCommunity). Start your own discussion with your questions or opinions on a topic of most interest to you. This is a global connection that can provide you with great perspectives and new ideas.

6. Get social! Join other CHEST members on Twitter, Facebook, or Instagram (www.chestnet.org/Get-Involved/Membership/Join/). Numbers 1-7 are just a few of the great opportunities you will have as part of the CHEST community. Good luck rebooting your resolutions! Now it’s time to work on one of my resolutions, less work on the weekends.

FROM THE EVP/CEO: ‘Global’ – more than a name for our new HQ

BY PAUL A. MARKOWSKI, CAE

After months of planning and much anticipation, we have moved to our new location in Glenview, Illinois. February 18 marked the first day in our new space, and there’s much to be proud of in this building. It won the prestigious “Green Development of the Year Award” for 2013 from the Commercial Real Estate Development Association, the premier organization for real estate professionals in metropolitan Chicago, and it’s under review for Silver LEED certification. It houses our state-of-the-art Innovation, Simulation, and Training Center, with an auditorium, eight breakout rooms, six simulation suites, and wet and dry labs to supplement training. Behind the scenes is an enhanced technological infrastructure to support digital learning. More than a beautiful structure with impressive features, this building is the resource we need to be the global leader in advancing best patient outcomes through innovative chest medicine education, clinical research, and team-based care. It’s fitting we have named our new building CHEST Global Headquarters.

For us, being global extends well beyond a name for the building. It’s what we are. A timely testament to this is our CHEST World Congress, taking place this month in Madrid, Spain, where more than 1,500 attendees and faculty from all regions of the world are sharing best clinical practices. We’ve partnered with the Spanish Society of Pneumology and Thoracic Surgery to develop the scientific program, ensuring topics presented are of educational value to an...
Continued from previous page

international audience. And, to keep the momentum of the Congress going, we’re already thinking about and planning for CHEST World Congress 2016.

Our other education programs, intended to have meaningful impact on global lung health and patient care, consistently prove to have high value for an international audience as well. Our CHEST annual meeting is always well attended by health professionals from around the world. CHEST 2013 was no exception, with 28% – or 1,450 – of the attendees coming from outside the United States and Canada. And, with CHEST endorsement currently being sought for education activities in other countries, from India to Italy, our global impact continues to reach beyond our annual meeting.

As part of our new brand promise to be an essential connection at a critical time, we are committed to delivering knowledge in formats that meet the needs of busy clinicians worldwide. CHEST Journal is an ideal medium for this, and more than 21,000 subscribers around the world receive it either in print or online. Various international editions have been published, including those for Brazil, China, Greece, India, Italy, the Middle East, Spain, and Turkey. These editions are published in each country’s native language, allowing health-care professionals to read and study the research in a language that is familiar and easily understood.

Our membership reflects our strong representation around the world. We have members in more than 100 countries, and almost 26% of our total membership is from outside the United States and Canada. Our Council of Global Governors, in place to promote leadership opportunities for international members, is operating strong at almost 30 governors. These leaders work to expand our education programs and membership, promote relationships with international industry partners, recruit attendees for CHEST activities, and more. This global community means more ideas, perspectives, and opportunities to collaborate and advance chest medicine around the world.

Over the next few months, we’ll be setting into our new CHEST Global Headquarters and establishing ourselves in our new neighborhood. Our presence across the world is already established, and I look forward to watching that grow as we leverage the resources available in our new building. Follow me on Twitter (@PMarkowskiACCP) to read our progress. And, if you’re in the Glenview, Illinois, area, stop by our new building. We’ll be happy to show you around.

This Month in CHEST: Editor’s Picks

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


Experiences of Racism and the Incidence of Adult-Onset Asthma in the Black Women’s Health Study. By Dr. P. F. Coogan et al.

Topics in Practice

Management


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WE’VE MOVED

The American College of Chest Physicians recently moved to its new CHEST Global Headquarters. We’ve built a 48,500-SF building to Silver LEED specifications, allowing us to:

- A center for innovative, interactive education.
- A catalyst for new ideas.
- An active partner in implementing and disseminating new clinical practices that benefit patients worldwide.

The building houses our state-of-the-art Innovation, Simulation, and Training Center for delivering clinical education and skills training in pulmonary, critical care, and sleep medicine.

You can now visit us at:

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224/521-9801 F

> Learn more about the training center at chestnet.org/center
**NEWS FROM CHEST**

**NETWORKS:** Seasonal disasters, e-cigs in smoke-free times, celebrating transplant anniversaries

**Disaster Response**

*Disaster events related to the winter season*

In this winter season we have seen snow, freezing rain, below zero temperatures, and ice storms along with high winds. This makes us more vigilant about the weather and its consequences both outside and inside our homes. This is especially true when ice storms disrupt powerlines, and large areas are without electricity or telephone service.

The first line of defense for storms is preplanning both for places of safety (warming centers, shelters, alternate care sites) and for a public awareness to reach these sites early before conditions become dangerous. A set of winter disaster materials (ie, extra blankets, boots, gloves, hats, flashlights, water, power bars, etc) should be available in place for both home and car. If your car becomes stranded on the highway, it is advised to stay with your car rather than hiking to find help. Mark your car so that highway patrol or snowplow drivers will see you.

The high-risk populations of the elderly and very young should always be suspected of some degree of hypothermia, frostbite, and carbon monoxide exposure if in a confined space indoors. Hypothermia can be classified as mild, moderate, or severe. The classification relates to the core body temperature (range 35-28 degrees C.). Arrhythmias, including fibrillation and bradycardia, along with tachycardia and hypotension, can be seen. Removal of wet clothing, rewarming, and following ACLS guidelines are starting points for care. Carbon monoxide poisoning should be treated with 100% oxygen.

Preparation and preplanning can be your best outcome in these winter months.


**Alan Roth, MS, NPS, RRT**

**Steering Committee Member**

**Women’s Health Network**

*ENDS of a smoke-free era*

The crux of the concern regarding unrestricted access of e-cigarettes to minors is this potential nicotine addiction. Adolescents have increased susceptibility to nicotine addiction (Dwyer et al. Pharmaco1 Ther. 2009;122(2):125). The proliferation of e-cigarettes or ENDS (electronic nicotine delivery systems) challenges decades of efforts to limit marketing to youth and public use of tobacco products (Fairchild et al. N Engl J Med. 2014;370(4):293). Efforts to prevent hard won gains from being undermined have been initiated. Locally, hospitals and college campuses have added e-cigarettes to smoke-free policies. Nationally, the US Food and Drug Administration has been asked to regulate e-cigarettes as tobacco products. ENDS may have a role as a smoking

Continued on following page
NetWorks’ abstract winners – CHEST 2013

For the past 2 years at CHEST, the NetWorks have identified and recognized outstanding abstracts.

This year, the NetWorks recognized 15 outstanding affiliate abstracts in the clinical areas of Allied Health, Cardiovascular Medicine and Surgery, Chest Infections, Clinical Pulmonary Medicine, Critical Care, Disaster Medicine, Interventional Chest/Diagnostic Procedures, Interstitial and Diffuse Lung Disease, Pediatric Chest Medicine, Pulmonary Physiology, Function, and Rehab, Pulmonary Vascular Disease, Respiratory Care, Sleep Medicine, Thoracic Oncology, and Transplant.

Their contributions to clinical research were recognized at the NetWork Featured Lectures during CHEST 2013.

NetWork: Allied Health
Abstract Title: Improving the Specificity of D-Dimer in Pulmonary Embolism
Presented to: Dr. Thomas Murphy

NetWork: Cardiovascular Medicine and Surgery
Abstract Title: Left Ventricular Diastolic Dysfunction Predicts Presence of Pleural Effusion Better Than Left Ventricular Ejection Fraction in Congestive Heart Failure
Presented to: Dr. Amita Kalra

NetWork: Chest Infections
Abstract Title: Characteristics and Outcomes Following Pulmonary Cryptococcosis in Solid Organ Transplantation: Comparison With Nonsolid Organ Transplant Patients
Presented to: Dr. Angel Brown

NetWork: Clinical Pulmonary Medicine
Abstract Title: The Prevalence of Obstructive Lung Pattern on Pulmonary Function Tests in Patients With Congestive Heart Failure
Presented to: Dr. Larry Ladi

NetWork: Critical Care
Abstract Title: Outcomes of Patients in the Marked Interval Recovery After Critical Illness With Low Expected Survival (MIRACLES) Study
Presented to: Dr. James Louiseill

NetWork: Disaster Response
Abstract Title: A Quality Improvement Project to Reduce Congestive Heart Failure Mortality With Intensive Case Management
Presented to: Dr. Pratik Dalal

NetWork: Interventional Chest/Diagnostic Procedures
Abstract Title: Pharmacokinetics of Paclitaxel Delivery for the Airway by a New Endobronchial Drug Delivery Catheter: Experimental Study
Presented to: Dr. Hisashi Tsukada

NetWork: Intstitial and Diffuse Lung Disease
Abstract Title: Hypersplenism and Polyrarthritis Are Strong Risk Factors for Common Variable Immunodeficiency Related Granulomatous-Lymphocytic Interstitial Lung Disease
Presented to: Dr. Richard Hedelius

NetWork: Pediatric Chest Medicine
Abstract Title: Delay to Diagnosis and Delay to Treatment in South African Children With MDR-TB and HIV
Presented to: Dr. Alfredo Lee Chang

NetWork: Pulmonary Physiology, Function, and Rehab
Abstract Title: The Effect of 6-Week Pulmonary Rehabilitation in COPD: A Randomized Control Study
Presented to: Dr. Deepu Cheriamane

NetWork: Pulmonary Vascular Disease
Abstract Title: Hemodynamic Effects of First-Line Bosentan and Sildenafil Combination Therapy for Pulmonary Arterial Hypertension
Presented to: Dr. Jason Weatherald

NetWork: Respiratory Care
Abstract Title: Positional Changes in Oxygen Saturation at High Altitude
Presented to: Dr. Chandra Patel

NetWork: Sleep Medicine
Abstract Title: Treatment Response in Patients With Opioid-Related Central Sleep Apnea
Presented to: Dr. Rooptika Reddy

NetWork: Thoracic Oncology
Abstract Title: The Impact of Microscopically Positive Final Pathologic Margins Identified Days After Surgery in Resected Non-small Cell Lung Cancer (NSCLC)
Presented to: Dr. David Odell

NetWork: Transplant
Abstract Title: Diffuse Alveolar Hemorrhage in Hematopoietic Stem Cell Transplant Recipients: 10-Year Experience in a Single Center
Presented to: Dr. Raolat Abdulai

Transplant
Lung transplantation: golden or pearl anniversary
It has been more than 50 years since the first attempt at human lung transplantation and over 30 years since the first success. The initial obstacles of graft preservation, surgical technique, and immunosuppression have been surmounted with continued refinement and ongoing identification of new challenges. Overall survival is 82% at 1 year, 55% at 5 years, and 31% at 10 years as reported in the October 2013 Registry Report of the International Society of Heart and Lung Transplantation. This registry reported over 3,700 lung transplants performed annually worldwide (in 2011) and a cumulative total of 40,000 since 1988. Close to 1,800 lung transplants are performed annually in the United States. This volume 10 years ago was approximately 1,000, 20 years ago, 700; and 25 years ago, 33 (Organ Procurement and Transplant Network Data as of February 7, 2014). Improved outcomes, increasing organ utilization, and more efficient and equitable allocation are evidence of success in this field. In clinical practice, the 5-, 10-, and 20-year “well-patient” visits are the reminders. A large part of this success reflects the ongoing improvements in the "craft" of transplantation and the maturation of a true multidisciplinary field encompassing surgery, medicine, anesthesia, critical care, nursing, radiology, pathology, immunology, pharmacology, social work, nutrition, respiratory therapy, and many others. Yet, the current survival statistics, as well as waiting-list volume and mortality, clearly demonstrate that we still have a long way to go.

Our knowledge of immune function and alloimmunity has grown exponentially. The relatively small number of lung transplants and limited funding pose significant challenges for the translational and clinical research critically necessary to evaluate outcomes and the application of scientific advances in the clinical arena. Lung transplantation occurs at a predictable volume and at a relatively small number of centers, and, thus, multicenter studies are feasible. As lung transplantation moves into its next half century, we must strive to pursue the learning and research opportunities necessary to achieve optimal and equitable allocation and outcomes.

Dr. Jeffery D. Edelman, FCCP
Steering Committee Member
COPD HUB

Bringing you the latest pulmonary medicine news.

Look to COPD Hub for all the cutting-edge news from medical meetings, the FDA, and medical specialty journals.

COPD Hub is powered by Frontline Medical Communications, the leader in medical specialty news for nearly 50 years.
CHEST 2014 opportunities

Abstracts and case reports – free submission

Submit an abstract of your original investigative work or a case report for presentation at the meeting. Categories are available for health professionals at all stages of their careers, including students and residents. Both domestic and international submissions are invited, and submission is free.

Call for abstracts
Submission deadline: April 1
Submit an abstract of your original investigative work for presentation at the meeting. Accepted abstracts will be published in an online supplement to CHEST. Three types of abstracts will be considered:
- Slide Presentations
- Poster Presentations
- NEW! Poster Discussions
Learn more and submit at chestmeeting.chest.net.org.

Call for case reports
Submission deadline: April 1
Submit case reports for presentation during special sessions. Accepted case reports (excluding clinical case puzzlers) will be published in an online supplement to CHEST. Four types of case reports will be considered:
- Affiliate Case Reports
- Medical Student/Resident Case Reports
- Global Case Reports
- Clinical Case Puzzlers
Learn more and submit at chestmeeting.chest.net.org.

The CHEST Foundation 2014 Grants and Awards Program
Application deadline: May 31
The CHEST Foundation tradition of recognizing and rewarding health-care professionals for scholarly projects, and clinical/translational research continues. Grants for both leaders in chest medicine and young investigators are available, including:
- GlaxoSmithKline Distinguished Scholar in Thrombosis—$150,000 over 3 years
- The CHEST Foundation Clinical Research Grant in Pulmonary Arterial Hypertension—$50,000 1-year grant
- The CHEST Foundation and the Pulmonary Fibrosis Foundation Clinical Research Grant in Pulmonary Fibrosis—$30,000 1-year grant
- CHEST Diversity Committee Young Investigator in Pulmonary, Cardiovascular, Critical Care, or Sleep Research Grant—$25,000 1-year grant
- Humanitarian/Community Service Grants
See which grants you are eligible for, and apply today at chestnet.org/grants.

Play CHEST Challenge
Game ends: May 30
CHEST affiliate members, play CHEST Challenge to test your knowledge of pulmonary, critical care, and sleep medicine while competing for prizes.

- The three top-scoring programs will compete in the CHEST Challenge Championship at CHEST 2014. All championship players will receive:
  - Airfare and registration to CHEST 2014 in Austin, Texas
  - Complimentary hotel
  - Cash prizes
- Game on! Log on and learn more at chestchallenge.org.

Road to ICD-10: What you should do to prepare

By Jeanna Stovall, MSA, RHIA
CHEST Regulations & Reimbursement Director

The October 1, 2014 deadline for ICD-10CM/PCS implementation is less than 8 months away. Whether your health centers ICD-10 preparations are on schedule, or if you are lagging behind, this article will provide useful information no matter what level of preparation your office has completed.

First, identify next steps:
- Have you completed an analysis of business impacts, to include end-to-end solutions for the following areas?
  - Coding training, billing, EHR (electronic health records), benefits and coding determinations, reimbursement, managed care contracts and auditing.
  - Talk with your payers about how ICD-10 implementation might affect your commercial managed care contracts. Since ICD-10 codes are much more specific, payers may modify terms of contracts, payment schedules, reimbursement, and coverage determinations.
  - Ensure the EHR system captures the correct ICD-10 code.
  - Go to https://implementicd10.noblis.org/ for detailed planning guides.
- Do you use billing software, clearinghouse, or billing service to submit claims? Or are you in the process of purchasing and/or contracting with a vendor? Is the vendor using HIPAA version 5010?
  - Call the vendor to determine level of compliance to ICD-10 standards, when upgrades and testing will be done (either at cost or no cost).
  - Schedule internal testing with the vendor to ensure your practice is able to send and receive transactions with ICD-10 codes.

Review internal standard operating procedures and policies to ensure all practice documents are up-to-date.

Second, see the chart below for a few translated ICD-9 to ICD-10 codes to begin the journey to success.

**ICD-9**

<table>
<thead>
<tr>
<th>ICD-10</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>J44.0 COPD</td>
<td>COPD with acute lower respiratory infection</td>
</tr>
<tr>
<td>J44.1 COPD</td>
<td>COPD with acute exacerbation</td>
</tr>
<tr>
<td>J44.9 COPD</td>
<td>COPD unspecified</td>
</tr>
<tr>
<td>J18.0 Pneumonia</td>
<td>Bronchopneumonia, unspec. organism</td>
</tr>
<tr>
<td>J18.1 Lobar pneumonia</td>
<td>unspec. organism</td>
</tr>
<tr>
<td>J18.2 Hypostatic pneumonia</td>
<td>unspec. organism</td>
</tr>
<tr>
<td>J18.6 Other pneumonia</td>
<td>unspec. organism</td>
</tr>
<tr>
<td>J18.8 Pneumonia</td>
<td>unspec. organism</td>
</tr>
<tr>
<td>J62.0 Pneumonia</td>
<td>Septic pulmonary embolism with acute cor pulmonale</td>
</tr>
<tr>
<td>J62.02 Saddle embolus of pulmonary artery with acute cor pulmonale</td>
<td></td>
</tr>
<tr>
<td>J62.09 Other pulmonary embolism with acute cor pulmonale</td>
<td></td>
</tr>
<tr>
<td>J62.80 Septic pulmonary embolism without acute cor pulmonale</td>
<td></td>
</tr>
<tr>
<td>J62.82 Saddle embolus of pulmonary artery without acute cor pulmonale</td>
<td></td>
</tr>
<tr>
<td>J62.89 Other pulmonary embolism without acute cor pulmonale</td>
<td></td>
</tr>
<tr>
<td>S32.71 Sleep apnea</td>
<td>Sleep apnea, unspecified</td>
</tr>
<tr>
<td>S47.30 Sleep apnea</td>
<td>Primary central sleep apnea</td>
</tr>
<tr>
<td>S47.31 Sleep apnea</td>
<td>High-altitude periodic breathing</td>
</tr>
<tr>
<td>S47.33 Obstructive sleep apnea (adult) (pediatric)</td>
<td></td>
</tr>
<tr>
<td>S47.34 Obstructive sleep-related nonobstructive alveolar hypoventilation</td>
<td></td>
</tr>
<tr>
<td>S47.35 Congenital central alveolar hypoventilation syndrome</td>
<td></td>
</tr>
<tr>
<td>S47.46 Sleep-related hypoventilation in conditions classified elsewhere</td>
<td></td>
</tr>
</tbody>
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Something new is in store – a new way to give to The CHEST Foundation

The next time you visit the online CHEST Store to register for a course, download an app, or purchase self-study materials, make sure to visit the new CHEST Foundation page. You will find the “Make A Gift” link at the bottom of the Bookstore Section. You can also access it directly at www.chestnet.org/store/donate.

Your unrestricted donations will help support the advancement of chest medicine through our ongoing programs and activities, including:
- Clinical research grants and awards.
- Youth tobacco prevention programs.
- Patient and public education.
- Community service and humanitarian programs.
- Join your colleagues and friends, and become a member of The CHEST Foundation Annual Giving Club. You will receive special recognition and benefits based on your level of giving.
- Please visit the CHEST Store today, and make a donation to become a member!
- Questions about making a gift to The CHEST Foundation? Please contact Patti Steele, Annual Fund Manager, at 224/521-9527 or psteele@chestnet.org.

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**Connect with your colleagues when you need them most!**

- Learn more about NetWorks: chestnet.org/NetWorks
- Log in to the e-Community: ecommunity.chestnet.org

NEWS FROM CHEST 2014
SLEEP MEDECINE MARCH 2014 • CHEST PHYSICIAN BY DR. LISA F. WOLFE, FCCP

The provision of home-based ventilatory support has been the purview of the pulmonologist for more than 50 years. Before the birth of sleep medicine as a dedicated specialty, the focus of home ventilation was on the care of patients with neuromuscular disease (NMD), who were required to use full-sized mechanical ventilators, nonvented masks, and bulky tubing sets with double-lumen active circuits served by an external pressure line, since this was the only equipment available at the time. These large devices were cumbersome and limiting in their lack of portability but were well suited to the needs of patients with NMD. They used volume-cycled ventilation, ensuring full ventilatory support with a guaranteed inspiratory time and respiratory rate. Although effective, they lacked many of the conveniences that are now the norm, including integrated humidifiers and a wide range of mask options.

In the 1980s, continuous positive airway pressure (CPAP) became widely available as therapy for OSA (Shepard et al. J Clin. Sleep Med. 2005;1[1]:61). The large number of patients with OSA spawned a revolution in home respiratory therapy, driven by a rapid expansion in resources, including the development of outpatient facilities dedicated to diagnosing and treating sleep-related breathing disorders, smaller and lighter equipment with novel ventilator modes, improved options for facial appliances, and other comfort-oriented features. While a new generation of practitioners pursued training in the management of sleep-disordered breathing, it was largely focused on OSA, with very limited experience managing the special needs of the NMD patient population.

Sleep laboratories often lacked the necessary amenities and frequently performed inappropriate diagnostic studies that delayed the time to initiation of noninvasive ventilation (NIV) for years, many clinicians caring for NMD patients avoided referring them to sleep programs, trying to provide care with minimal support from pulmonary physicians. For example, although the American Academy of Neurology recommends the use of NIV as standard of care for patients with amyotrophic lateral sclerosis, they do not recommend the involvement of a sleep laboratory, choosing instead to rely upon guidance from pulmonary function testing (Miller et al. Neurology. 2009;73[15]:1218). This recommendation is based on several studies, including a prominent randomized control trial, which demonstrated a mortality and quality of life benefit from NIV, though it did not use polysomnography to optimize the treatment (Bourke et al. Lancet Neurol. 2006;5[2]:140). For years, many clinicians caring for NMD patients avoided referring them to sleep programs, trying to provide care with minimal support from pulmonary physicians. In a survey of Muscular Dystrophy Association clinics from 2000, polysomnography was only provided by a third of programs; the authors subsequently call the procedure unnecessary, as well as “uncomfortable and often painful” (Bach and Chaudhry. Am. J. Phys. Med. Rehabil. 2000;79[2]:193).

Advances in sleep medicine therapeutics

New developments seem likely to bring these previously discordant groups into a more harmonious relationship, driven by changes on two fronts. First, the role of the sleep lab is changing, as home sleep testing combined with auto-titrating CPAP machines play a larger role in the management of OSA. For brick-and-mortar labs needing to reinvent themselves, one option is to expand care to aggressively address the needs of those with non-OSA forms of sleep-disordered breathing, including nocturnal hypoventilation due to NMD. Though less prevalent, these conditions will continue to require in-lab sleep testing, although labs will need to adapt to meet the additional needs of these patients, as outlined in Table 1. The physical design of the lab will need to better accommodate power chairs, with additional space for caregivers. Polysomnographic technologists will need to have equipment to facilitate bed-to-chair transfers. Respiratory assist device options will need to be expanded to include those more capable of supporting ventilation, while study montages will need to include parameters to better assess ventilation, work of breathing, and/or accessory muscle use. Lastly, labs will need to develop more productive relationships with durable medical equipment providers to help them understand that patients with NMD have different needs than those with OSA.

The second major development that may allow sleep providers to better service these patients is the advent of new technology for home-based ventilation. Many of the advantages previously available only with CPAP devices have now been made available for use with noninvasive ventilators. These new NIV devices are smaller, and use lighter, single-lumen passive circuits that can utilize any of the commonly available CPAP masks instead of requiring...
**South Florida Critical Care Medicine - Nocturnist**

**About the Opportunity:**
Memorial Healthcare System’s Intensivist program is expanding. The program is currently comprised of 21 full-time intensivists, providing 24/7 ICU coverage at multiple locations within The Memorial Healthcare System. In addition to critical care, many of our intensivists hold multiple Board Certifications in infectious diseases, pulmonology, surgery and neuro-critical care. This is a full-time employed position with competitive benefits and compensation package. “Sovereign immunity,” paid CME, state of the art equipment (including EPIC EMS, digital Olympus bronchoscopes, intubation scopes, Echocardiography, Sonosite Ultrasounds etc).

**Qualifications & Responsibilities:**
The program is seeking four (4) dedicated critical-care nocturnists to join the existing team. The nocturnists will integrate into the existing operational structure as the program expands to cover additional critical care units. Critical care coverage is provided in 12 hour in-hours shifts, 7pm to 7am – averaging approximately 15 shifts per month. The successful candidates will have excellent clinical skills, a broad knowledge base in critical care and be dedicated to providing high quality, evidence based care. Candidates must be BC/BE.

**About Memorial Healthcare System:**
Memorial Healthcare System is a 1,900-bed healthcare system located in South Florida and is highly regarded for its exceptional patient- and family-centered care. Memorial’s patient, physician and employees satisfaction rates are among the most admired in the country, and the system is recognized as a national leader in quality healthcare.

**About South Florida:**
South Florida offers quality of life, is rich in cultural and recreational amenities, and offers pristine beaches, top-rated golf courses, museums and world-class dining. The greater Ft. Lauderdale area offers numerous communities in which to raise a family. In addition, Florida has no state income tax.

To inquire about this opportunity, visit memorialphysician.com

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**California**

Coastal Suburban Southern CA

Seeking a BC/BE CCM physician to join a well-respected Intensivist Program in Pulmonary and Critical Care Medicine to serve as Fellowship Director. All candidates must have an established record of scholarship and mentoring of junior faculty. ETSU is an AA/EEO employer.

View position summary and apply at https://jobs.etsu.edu/applicants/jsp/shared/Welcome.jsp

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**New York**

St. Barnabas Hospital, a Level 1 Trauma Center in the Bronx, New York has great opportunities for Critical Care Physicians to practice in a multi-disciplinary ICU.

We are looking for a full time employee who have part-time and per-diem work available as well.

Please fax CV to: 718-960-6122.

---

**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/EEO employer.

View position summary and apply at https://jobs.etsu.edu/applicants/jsp/shared/Welcome.jsp

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**South Carolina**

Pulmonary Opportunity in Upstate, SC

- BC/BE pulmonologist needed for employed practice
- Call: 7
- State-of-the-art technology including: Navigation bronchoscopy, bronchial thermoplasty, Video-assisted thoracic surgery, endobronchial ultrasound, brachytherapy, stents, peripheral bronchoscopy.
- Office has x-ray, lab, PFTs and adjacent sleep lab.
- Rotate weeks between the hospital and office; office week: 4 half days with 12-15 patients/day; Hospital week: full call every other day with half office days in between.

Anderson is located in the northwest corner of South Carolina near beautiful Lake Hartwell and the foothills of the Blue Ridge Mountains. Lake front property is very affordable. The area offers excellent public and private schools, as well as cultural opportunities associated with Anderson and Clemson Universities.

Contact Brandy Vaughn: brandy.vaughn@annmedhealth.org (864) 512-3897

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**New Mexico**

San Juan Regional Medical Center in Farmington, NM is recruiting a Pulmonologist to join The San Juan Regional Heart Center with a focus on pulmonary hypertension and right heart catheterizations and will participate in acute consults.

This is a Hospital-employed, cardiovascular practice setting with a competitive compensation plan, benefit package, relocation, and a sign-on bonus.

Contact Terri Smith: 888-282-6551 tsmith@sjrmc.net

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**Kentucky**

Employed opportunity for a BC/BE Pulmonary Critical Care. This practice includes outpatient and in-patient based practice plus a Medical Director opportunity.

Contact: Ceil Baugh, MSHRM Baptist Health Madisonville Ceil.Baugh@bshi.com 270-326-4520

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**Huntsville Hospital • Huntsville, Alabama**

Seeks a Pulm/CC Physician Immediately!
- Established, hospital-owned practice
- Employment w/excellent compensation package
- 101 open ICU beds
- 881 bed Level I Trauma/Regional Referral Center
- Teaching opportunity with UAB
- Huntsville named in Forbes list of Top Ten Smartest Cities in the World

Interested physicians should contact: Kimberly Salvail, Huntsville Hospital – Kimberly.salvail@hhsys.org or 256-285-7073.

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**ARIZONA**

Outstanding opportunity in metro Phoenix area. Practice includes all aspects of pulmonary medicine including sleep and critical care. Excellent opportunity for a new graduate or physician looking to make a lateral move.

Please forward CV via fax to 480-655-1640 Attn: Cathy or via email to cpatzke@azlungcenter.com
Pregabalin improves RLS with less augmentation

BY MARY ANN MOON
Frontline Medical News

oral pregabalin significantly improved symptoms of moderate to severe restless leg syndrome, compared with both placebo and pramipexole, in an industry-sponsored, international randomized trial.

Just as important, pregabalin was associated with significantly less iatrogenic worsening, or augmentation, of symptoms than was pramipexole, Richard P. Allen, Ph.D., of the department of neurology at Johns Hopkins University, Baltimore, and his associates reported in the New England Journal of Medicine.

Pregabalin also was associated with lower rates of nausea, vomiting, and headache than pramipexole, but patients taking pregabalin had higher rates of suicidal ideation, dizziness, somnolence, and weight gain — “factors that may limit its long-term use,” the investigators said.

Dopaminergic drugs such as pramipexole are known to be associated with augmentation in which symptoms intensify and may involve more parts of the body and start earlier in the day than before treatment. Pregabalin is a nondopaminergic agent with analgesic and anticonvulsant activity, and was recently reported to be effective against restless leg syndrome.

Dr. Allen and his colleagues assessed both agents in a study involving 719 adults with moderate to severe primary restless leg syndrome. The patients did not undergo an objective assessment of sleep.

In the double-blind trial sponsored by Pfizer, the manufacturer of pregabalin, these patients were randomly assigned to receive 0.25 mg pramipexole, 0.5 mg pramipexole, 300 mg pregabalin, or matching placebo capsules every day for 12 weeks. At that time, all patients receiving placebo were randomly reassigned to one of the three active treatments for the remainder (40 weeks) of the 1-year study. The mean age of the patients ranged from 54 to 77 years in the groups.

Periodically, participants reviewed with clinicians their daily symptom logs and completed the International RLS (IRLS) Study Group Rating Scale, which measures subjective symptom severity on a 0-40 scale, with higher scores indicating worse symptoms.

Clinicians also assessed patients’ symptoms using the Clinical Global Impression of Improvement (CGI-I) scale, and they assessed possible augmentation using their clinical judgment, scores on the Augmentation Severity Rating Scale, and scores on the Structured Interview for the Diagnosis of Augmentation instrument.

At 12 weeks, patients who received pregabalin showed significantly greater improvement in IRLS scores than did those who received placebo, improving from 22.3 to 10.9 for pregabalin-treated patients and from 22.4 to 15.5 for placebo-treated patients. Pregabalin-treated patients also were more likely to have “very much improved” or “much improved” ratings on the CGI-I, compared with placebo (71.4% vs 46.8%).

Patients who received pregabalin also reported greater improvement in several sleep parameters, including waking after sleep onset, quality of sleep, and total sleep time, compared with those who received placebo. These measures also were significantly better for patients treated with 0.5 mg pramipexole when compared with placebo-treated patients, but not for those taking 0.25 mg pramipexole.

The finding that pregabalin is effective for RLS even though it has no direct effect on dopaminergic systems calls into question the rationale for dopaminergic therapies. Dopaminergic treatments have been predicated on the assumption that RLS results primarily from dopamine abnormalities, Dr. Allen and his associates noted (N. Engl. J. Med. 2014 Feb. 12 [doi:10.1056/NEJMe1313155]).

Pregabalin was associated with significantly less augmentation than the 0.5-mg dose of pramipexole, but not the 0.25-mg dose. Among patients receiving active treatment over the entire 52-week study period, augmentation occurred in 3 of 176 patients receiving pramipexin (1.7%), 11 of 167 receiving 0.25 mg of pramipexole (6.6%), and 16 of 178 receiving 0.5 mg of pramipexole (9.0%), the investigators wrote.

Dr. Allen reported ties to Pfizer, UCB Pharma, Impax Pharmaceuticals, Luitpold Pharma, Xenopont, Glaxo-SmithKline, and Pharmacosmos. His associates reported ties to Pfizer and numerous industry sources. Four authors are employees of Pfizer.

VIEW ON THE NEWS

This carefully conducted study is one of a few head-to-head studies of two classes of medications that have been reported for the treatment of restless leg syndrome. It presents compelling evidence for the efficacy of a nondopaminergic drug in the treatment of RLS and thereby implicates a role for nondopaminergic pathways in the disease, said Dr. Sudhansu Chokroverty.

Although augmentation occurred significantly more often with pramipexole, patients who took pregabalin still had a rate of 1.7%, which “raises the question of whether augmentation is related to medication, is intrinsic to RLS, or is related to individual patient characteristics,” he noted.

Dr. Chokroverty is with the department of neurology at the New Jersey Neuroscience Institute, JFK Medical Center, Edison. He reported no relevant financial conflicts of interest. These remarks were taken from his editorial accompanying Dr. Allen’s report (N. Engl. J. Med. 2014 Feb. 12 [doi:10.1056/NEJMe1313155]).

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FDA approves tasimelteon for sleep-wake disorder

BY ALICIA AULT
Frontline Medical News

The U.S. Food and Drug Administration approved tasimelteon (Hetlioz) for sleep disturbances in the blind.

The drug, a melatonin receptor agonist, is indicated only for totally blind individuals who have chronic non-24-hour sleep-wake disorder.

With non-24, as it is called, the circadian rhythm is disrupted, causing difficulty with the timing of sleep. People who have the condition sleep when they should not and can’t sleep when they should.

“Non-24-hour sleep-wake disorder can prevent blind individuals from following the normal daily schedule that we all take for granted,” said Dr. Eric Bastings, deputy director of the division of neurology products in the FDA’s Center for Drug Evaluation and Research, Silver Spring, Md. “Hetlioz can improve the ability to sleep at night and to be active during the day.”

The FDA and tasimelteon’s maker, Vanda Pharmaceuticals, estimate that 80,000-100,000 blind individuals have non-24 disorder.

Tasimelteon was given priority review by the FDA because it was deemed to have the potential to significantly improve patients’ lives.

Non-24 also is considered a rare condition, so tasimelteon received orphan-drug designation by the FDA, which gives it additional years of market exclusivity.

“Totally blind people have struggled with the problems brought on by non-24-hour sleep-wake disorder, sometimes for their entire life, without understanding what causes it and without being able to do anything about it,” said Steven W. Lockley, Ph.D., of the sleep medicine division at Brigham and Women’s Hospital, Boston, and an investigator for Vanda. The approval “means that, for the first time, these patients have access to an approved, safe and effective treatment for their difficult debilitating disorder,” Dr. Lockley said in a statement issued by Vanda.

The company evaluated tasimelteon’s effectiveness in 104 participants in two clinical trials of totally blind individuals with non-24 disorder. Patients receiving the therapy had significantly increased nighttime sleep and decreased daytime sleep duration, compared with placebo, according to the FDA.

The most common side effects were headache, elevated liver enzymes (alanine aminotransferase), nightmares or unusual dreams, disturbed night’s sleep, upper respiratory or urinary tract infection, and drowsiness. To reduce the risk of decreased mental alertness, the agency said, tasimelteon should be taken at the same time every night before bedtime and activities should be limited after taking the drug.

Vanda said that tasimelteon should be available within a few months as a 20-mg capsule. The company also has studied the drug for chronic insomnia and depression. It ended the depression studies in early 2013 and is not currently actively pursuing the insomnia indication.

Continued from page 28

The implementation of standardized protocols for VAPS titration would require a fundamental shift in the way polysomnographic technologists understand positive airway pressure treatments.

becomes more realistic for all patients with NMD.

New NIV devices are designed to specifically address problems of hypoventilation; these devices allow provisions for assured inspiratory times and respiratory rates, just like home-based mechanical ventilators. This is important because diaphragmatic fatigue, due to muscle weakness in neuromuscular patients, may present with either failure to initiate breaths or premature termination of breathing efforts. To completely support the work of breathing, these devices must be able to control the frequency and length of breath delivery. The new NIV devices have also been fitted with microprocessors and servo-motors that allow them to target specific volumes and minute ventilations. Referred to as volume-assured pressure support devices (VAPS, see Table 2), these machines offer a fresh perspective on autotitrating technology; rather than targeting patency of the upper airway just as traditional autotitrating PAP devices do, VAPS software measures markers of ventilation and augment support until pre-set targets are achieved.

The implementation of standardized protocols for VAPS titration would be a fundamental shift in the way polysomnographic technologists understand positive airway pressure treatments, targeting an adequate ventilation rather than patency of the upper airway. Such a protocol would require the technologist to set a pressure support range with a target tidal volume, inspiratory time, and respiratory rate. In addition, end-tidal carbon dioxide levels and respiratory muscle effort would need to be monitored throughout the study, with subsequent tweaking of the range of pressure support and expiratory pressure for hypoventilation and upper airway obstruction, respectively. Once the titration is complete, implementation of VAPS at home should help to compensate for fluctuations in disease severity and variability of hypoventilation with sleep stage and body position (Jaye et al. Eur Respir J. 2009;33(3):566). These devices also have internal batteries allowing for daytime use and can support noninvasive ventilation in a portable fashion using a mouthpiece, which can be set to deliver breaths on demand, allowing “off time” for coughing, swallowing, or speech.

Conclusion

Advancements in technology will foster a healthier relationship between sleep medicine and providers that treat neuromuscular disease, ushering in a new generation of sleep specialists and labs that can address sleep-related breathing disorders other than obstructive sleep apnea. While caring for these individuals will initially be a challenge to some of us who have been in practice for years, it is a natural extension of the medicine we have allways practiced and will lead to improved provision of care to and quality of life for some of our sickest patients.

Dr. Wolfe is Associate Professor in Medicine - Pulmonary and Neurology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois.

Scan the code for more Sleep Strategies columns at chestphysician.org.

Table 2: Options in Volume Assured Pressure Support (VAPS)

<table>
<thead>
<tr>
<th>Device</th>
<th>Manufacturer</th>
<th>Modes</th>
<th>Target of Ventilation</th>
<th>Unique Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average volume</td>
<td>Philips Respironics</td>
<td>S, ST, and PC</td>
<td>Tidal volume</td>
<td>Rate of change is adjustable</td>
</tr>
<tr>
<td>assured pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>support devices</td>
<td>Philips Respironics</td>
<td>S, ST, and PC</td>
<td>Tidal volume</td>
<td>Rate of change is adjustable</td>
</tr>
<tr>
<td>Intelligent</td>
<td>ResMed</td>
<td>ST</td>
<td>Alveolar ventilation</td>
<td>Trigger and cycle adjustments</td>
</tr>
<tr>
<td>volume</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>assured pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>support devices</td>
<td>Philips Respironics</td>
<td>S, ST, PC, MPV,</td>
<td>Tidal volume (upper airway pressure with AE)</td>
<td>Integrated battery backup</td>
</tr>
<tr>
<td>Upper airway</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>auto-ST</td>
<td>Weimann</td>
<td>S/ST</td>
<td>Upper airway pressure, respiratory rate, and tidal volume</td>
<td>Not available in the U.S.</td>
</tr>
<tr>
<td>Trilogy</td>
<td>Philips Respironics</td>
<td>S, ST, PC, MPV,</td>
<td>Tidal volume (upper airway pressure with AE)</td>
<td>Integrated battery backup</td>
</tr>
</tbody>
</table>

S = spontaneous, ST = spontaneous timed, PC = pressure control, MPV = mouthpiece ventilation
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