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CHEST™ Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

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"People are not as aware as they need to be about what antibiotics kill what bacteria," says the CDC's Dr. Arjun Srinivasan.

Redundant antibiotics flow at most hospitals

BY JENNIE SMITH
Frontline Medical News

Redundant combinations of intravenous antibiotics are used in nearly 8 of 10 hospitals, even though they are very infrequently indicated, said a group of researchers working to promote antimicrobial stewardship in hospitals.

Leslie Schultz, R.N., Ph.D., of Premier Safety Institute in Charlotte, N.C., and colleagues reported that a review of cases from more than 500 U.S. hospitals revealed that about 150,000 days of inappropriate antibiotic therapy were prescribed, at an estimated excess cost of more than $12 million over the 4-year study period. Some 78% of hospitals in the study used the unnecessary drug combinations, they said.

The combination of metronidazole and piperacillin-tazobactam accounted for more than half of the redundant treatments detected in the study, with some 32,500 cases receiving this combination for 2 days or more. Other commonly seen redundant treatments included metronidazole and ampicillin-sulbactam, along with metronidazole and ertapenem, which, together with the metronidazole and piperacillin-tazobactam combination, were seen as responsible for 70% of redundant treatments

See **Antibiotics** • *page 7*

Long-term benzo use linked to increased Alzheimer's odds

Higher half-life drug choices raise risk.

BY JENNIE SMITH
Frontline Medical News

Benzodiazepine use for 3 months or more is associated with a significantly increased likelihood of developing Alzheimer's disease, and longer exposure is associated with greater odds, according to results from a case-control study published in BMJ.

The authors, led by Sophie Billioti de Gage of Université de Bordeaux (France), conducted a nested case-control study of 1,796 members of a public drug plan in Quebec aged 66 years and older who had been diagnosed with Alzheimer's disease at least 6 years prior, and more than 7,000 non-Alzheimer's controls matched for age and sex.

Ms. Billioti de Gage and her colleagues found a cumulative dose-effect association between exposure to benzodiazepines at least 5 years before diagnosis and the odds of developing Alzheimer's disease, with a significantly greater likelihood observed with benzodiazepine use of 90 or more consecutive days (adjusted odds ratio, 1.51; 95% confidence interval, 1.36-1.69) and daily exposure to benzodiaze-

See **Benzodiazepine** • *page 18*

INSIDE

CRITICAL CARE COMMENTARY

ARDS: The past, present, and future

BY DR. MARTIN E. WARSHAWSKY, FCCP

Acute respiratory distress syndrome, or ARDS, was first recognized during wars of the 20th century and was referred to as shock lung. It was observed in association with trauma and was frequently fatal. The syndrome has also been observed in association with sepsis, pancreatitis, burns, trauma, toxic inhalation injury, thermal inhalation injury, major surgery, blood transfusion, shock, immune-mediated lung injury, and reaction to medication. Advances in support of the critically ill patient have improved survival in ARDS. Methods of providing

See **ARDS** • *page 16*

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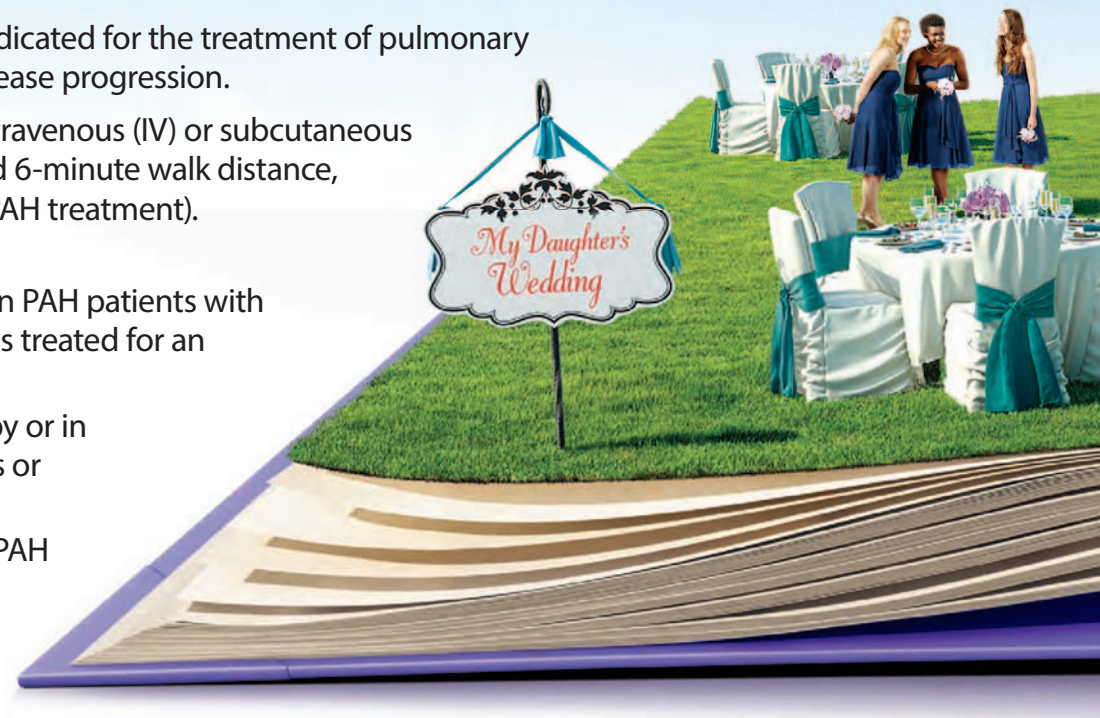
In the treatment of pulmonary arterial hypertension (PAH, WHO Group I)

HELP HER WRITE FUTURE CHAPTERS

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

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

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



IMPORTANT SAFETY INFORMATION

BOXED WARNING: EMBRYO-FETAL TOXICITY

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Embryo-fetal Toxicity and OPSUMIT REMS Program

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

Notable requirements of the OPSUMIT REMS Program include:

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

Hepatotoxicity

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

Patient dramatization

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

Hemoglobin Decrease

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

Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)

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

Decreased Sperm Counts

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

ADVERSE REACTIONS

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

DRUG INTERACTIONS

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

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

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macitentan tablets 10 mg

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Opsumit®
macitentan tablets 10 mg

Rx only

BRIEF SUMMARY

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

WARNING: EMBRYO-FETAL TOXICITY

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

INDICATIONS AND USAGE

Pulmonary Arterial Hypertension

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

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

CONTRAINDICATIONS

Pregnancy

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

WARNINGS AND PRECAUTIONS

Embryo-fetal Toxicity

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

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

OPSUMIT REMS Program

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

Notable requirements of the OPSUMIT REMS Program include the following:

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

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

Hepatotoxicity

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

Table 1: Incidence of Elevated Aminotransferases in the SERAPHIN Study

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

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

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

Hemoglobin Decrease

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

Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)

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

Decreased Sperm Counts

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

ADVERSE REACTIONS

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

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

Clinical Trial Experience

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

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

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

Table 2: Adverse Reactions

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

DRUG INTERACTIONS

Strong CYP3A4 Inducers

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

Strong CYP3A4 Inhibitors

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category X.

Risk Summary

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

Animal Data

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

Nursing Mothers

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

Pediatric use

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

Geriatric use

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

Females and Males of Reproductive Potential

Females

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

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

Males

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

OVERDOSAGE

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

CLINICAL PHARMACOLOGY

Pharmacokinetics

Special Populations

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

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

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

OPSUMIT® (macitentan)

Drug Interactions

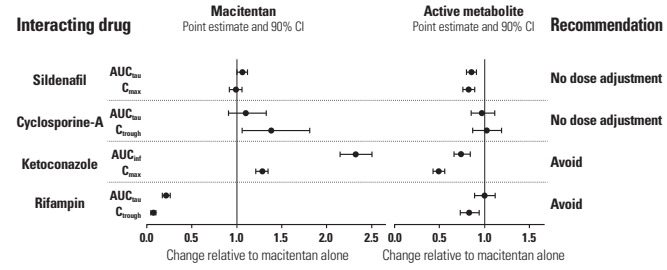
In vitro studies

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

In vivo studies

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

Figure 1



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

Effect of macitentan on other drugs

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

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

Animal Toxicology

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

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

Manufactured for:
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South San Francisco, CA 94080, USA
ACT20131018

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

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Meta-analysis: Pneumococcal vaccine protects against cardiac and cerebrovascular events

BY BRUCE JANCIN
Frontline Medical News

BARCELONA – Influenza vaccine has been shown to provide protection against cardiovascular events, but can the same be said for pneumococcal vaccine?

Yes, particularly in the elderly and in patients at high baseline cardiovascular risk, according to a meta-analysis presented by Dr. Dimitrios Terentes-Printzios at the annual congress of the European Society of Cardiology.

He analyzed 11 published studies comprising 332,267 subjects followed for a mean of 20 months. Because the studies focused on different populations and in some cases reached conflicting conclusions, he performed a series of subgroup analyses to gain a clearer picture.

One of these analyses found that the cardioprotective effects of pneumococcal vaccination wane over time. In studies with follow-up of less than 1 year, the relative risk of total cardiovascular events was 0.72, meaning that patients who received pneumococcal vaccine had a significant 28% relative risk reduction compared with those who did not. In studies with follow-up in excess of 1 year, however, there was no cardioprotective effect, according to Dr. Terentes-Printzios of Athens Medical School.

Significant protection against total cardiovascular events was seen in elderly vaccinated patients, with a 20% relative risk reduction, and in subjects at high baseline cardiovascular risk, who had an 8% risk reduction if they received pneumococcal vaccine.

Breaking down the specific endpoints, subjects who got pneumococcal vaccine had a statistically significant 8% reduction in the risk of cardiovascular mortality. However, vaccination provided no significant protective effect against acute MI or cerebrovascular events except in the elderly, where the relative risk reductions were 10% and 14%, respectively.

These cardio- and cerebrovascular protective benefits of the pneumococcal vaccine can be viewed as added value, given that the primary reason physicians prescribe the vaccine is its demonstrated ability to reduce the risk of invasive pneumococcal infection by up to 60%.

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VITALS

Key clinical point: Pneumococcal vaccine provides ancillary cardio- and cerebrovascular protective benefits, particularly in the elderly.

Major finding: Patients who got the pneumococcal vaccine had a statistically significant 8% reduction in the risk of cardiovascular mortality.

Data source: A meta-analysis of 11 studies comprising more than 332,000 patients.

Disclosures: Dr. Terentes-Printzios reported having no conflicts of interest regarding this study.

IN THIS ISSUE

Dr. W. Michael Alberts, FCCP, is Medical Editor in Chief of CHEST Physician.

VIEW ON THE NEWS

Dr. Jun Chiong, FCCP, comments: Many patients with pneumonia are known to be at increased risk for cardiovascular events. The American Heart Association's Get With The Guidelines – Resuscitation database found that in many stroke and cardiopulmonary arrests, pneumonia was a preexisting condition or was acquired during hospitalization.

Hence, it's expected that preventing pneumonia with vaccination will also prevent subsequent death from cardiovascular reasons. Pneumonia vaccination will prevent not only cardiovascular events but death in general.

This study found more compelling reasons for us in the front line to vaccinate eligible candidates for flu and pneumonia, especially with fall already here.

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A steady drip of duplicate drugs

Antibiotics *from page 1*

administered to patients (Infect. Control Hosp. Epidemiol. 2014;35:1229-35).

In a telephone press conference, one of Dr. Schultz's coauthors on the paper, Dr. Arjun Srinivasan of the Centers for Disease Control and Prevention, Atlanta, said that, while concerns about antimicrobial stewardship are not new, the findings came as a surprise. "We would expect the use of these combinations to be vanishingly rare given how often they're indicated," Dr. Srinivasan said, citing a lack of training in antibiotics as a contributing factor.

"We've heard from a lot of clinicians that providers don't know that piperacillin-tazobactam very effectively kills anaerobic bacteria – but they do know that metronidazole is effective," Dr. Srinivasan said. "People are not as aware as they need to be about what antibiotics kill what bacteria, and we need to make sure people know which antibiotics need to be combined and when – and that with some, you don't gain anything by adding the second drug. You only increase the risk of side effects."

Another physician taking part in the press conference, Dr. Sara Cosgrove of Johns Hopkins Hospital, Baltimore, agreed. "We have suboptimal training among medical students and house staff about what antibiotics cover what bugs," she said. "We have seen publications suggesting that medical students and residents want more info on antibiotics."

Dr. Cosgrove also noted that changes in hospital work practices may have contributed to the problem. "More people are working in hospitals on shorter shifts, and there are communication issues from one physician to the next. One physician may start an antibiotic and a second physician starts a second. There are many ways we can address the problem of unintended duplicate therapy," she said, including the use of alerts generated when pharmacy receives a request for a redundant drug.

Dr. Srinivasan said that hospitals that have implemented alerts have found them effective. Still, both physicians stressed that whatever the methods used, dedicated antimicrobial stewardship teams in hospitals were essential to ensuring the avoidance of redundant treatments.

"Many hospitals report that they are thinking about having an antimicrobial stewardship program. We'd like to nudge them to actually have one," said Dr. Cosgrove, who is chair of the antimicrobial stewardship committee for the Society for Healthcare Epidemiology of America, which publishes Infection Control and Hospital Epidemiology.

Though Johns Hopkins has had an antimicrobial stewardship team since 2002, most hospitals do not have formal groups in place, she said. The Society for Healthcare Epidemiology of America will publish checklists and guidelines in 2015 to help hospitals set up teams, Dr. Cosgrove said, noting that California has recently passed legislation mandating their creation in all hospitals in that state.

All the coauthors of Dr. Schultz's study except Dr. Srinivasan are employees of Premier, a for-profit research corporation. Dr. Srinivasan reported having no conflicts of interest.

VIEW ON THE NEWS

Dr. Steven Q. Simpson, FCCP, comments: To be honest, before reading this article, I expected the study to find problems with prolonged coverage for presumed MRSA with vancomycin or linezolid, or double anti-pseudomonal coverage when it is not necessary. I was

not expecting such a basic mistake as failure to recognize that penicillins and carbapenems provide excellent anaerobic coverage. Clearly, the medical students are correct in wanting more antibiotic training, and practicing physicians throughout the United States should follow suit with CME. Fortunately, antibiotic charts are readily available from a variety of reliable Internet resources, making this information easy to find and to use.

Resistant infection risk grows by 1% per hospitalization day

FRONTLINE MEDICAL NEWS

John A. Bosso, Pharm.D., explains how clinicians can reduce infection risks.

WASHINGTON – Each day of hospitalization increases the likelihood of contracting an infection with a gram-negative, multidrug-resistant organism by 1%, with risk maximizing at 10 days of hospitalization, said John A. Bosso, Pharm.D., a professor in the College of Pharmacy at the Medical University of South Carolina, Charleston. His research team analyzed 949 incidents of documented gram-negative infection during 1998-2014. The study is the first to quantify the potential risk of contracting a multidrug-resistant infection based on length of stay.

Dr. Bosso, who presented at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy 2014, said clinicians should be sure to advise patients on the risks associated with long hospital stays and encourage patients to do their part in getting out of the hospital as quickly as possible.

–Mike Bock

Fluoroquinolone bested other antibiotics in *H.influenzae* CAP

BY WHITNEY MCKNIGHT
Frontline Medical News

WASHINGTON – For adults with *Haemophilus influenzae*-related community-acquired pneumonia, fluoroquinolones were significantly associated with early clinical response rates that were better than those seen with other antibiotics, based on the findings of a German study.

"Initial treatment with any fluoroquinolone was the only positive predictor of early clinical response, and use of macrolide monotherapy was the only negative predictor of early clinical response," Dr. Christina Forstner, a researcher at the Medical University of Vienna in Austria, said at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy.

The multicenter, observational, prospective, cohort study was conducted between 2002 and 2012 in 171 adults who had community-acquired pneumonia and tested positive for *H. influenzae*. In 124 patients, *H. influenzae* was the sole pathogen detected, whereas 47 patients had at least one other coinfection.

The primary end point of the study was an early clinical response – clinical stability by day 4 of treatment. The secondary end point was clinical cure anywhere at day 14. The choice of antimicrobial treatment was left to the discretion of individual clinicians.

Early clinical response rates were seen for 46 of 47 patients (97.6%) given any fluoroquinolone, with

Early clinical response rates were seen for 46 of 47 community-acquired pneumonia patients (97.6%) given any fluoroquinolone, with 100% clinical cure by day 14.

100% clinical cure by day 14. Fluoroquinolone monotherapy achieved a nearly 100% early clinical response rate (39 out of 40 patients), and complete clinical cure was seen in all patients by day 14. The rates were significantly different from

Continued on following page

Continued from previous page

those seen with other antibiotics ($P = .01$).

An early clinical response rate was seen in 92 of 108 patients (85.2%) given any beta-lactam. Beta-lactam monotherapy achieved an early clinical response rate in 63 out of 74 cases, with a clinical cure rate at day 14 in 68 out of 74 cases.

An early clinical response rate was seen in 29 of 36 patients (80.6%) who received any macrolide; an early clinical response rate was seen in 8 of 12 patients given monotherapy with a macrolide. Clinical cure rate at day 14 was 32 out of 36 patients given any macrolide, and 11 out of 12 given macrolide monotherapy.

The median duration of therapy was, according to Dr. Forstner, "quite long" at 10 days. Monotherapy was used in 78.4% of patients, and oral treatments in 63.7%.

The overall early clinical response rate was 88%, with an overall clinical cure of 93% on day 14, and of 95.9% on day 28.

A univariate analysis of age, body mass index, severity of disease, coinfection, and treatments used indicated the only factor associated with an early clinical response was the use of any fluoroquinolone (odds ration, 8.8). Macrolide monotherapy was associated with a negative clinical response (OR, 0.239).

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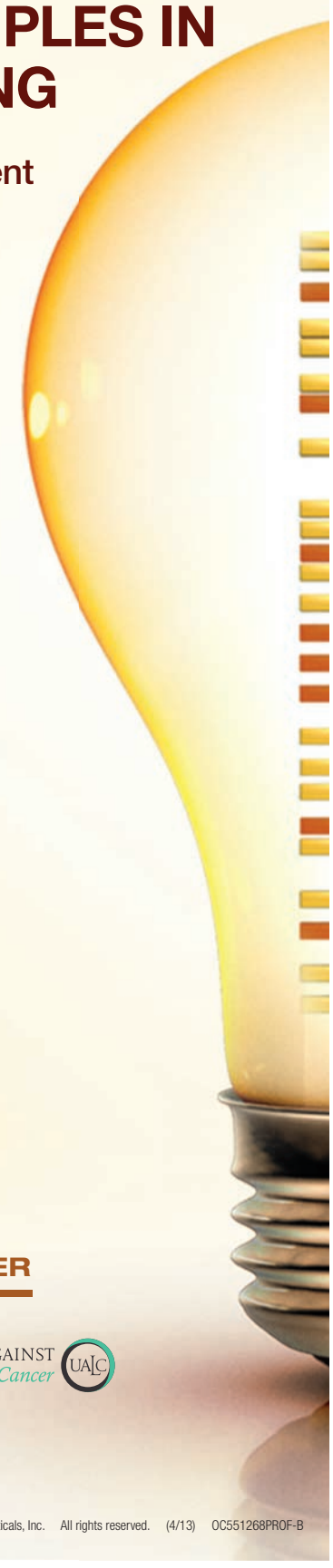

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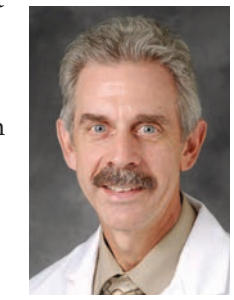
VIEW ON THE NEWS

Dr. Daniel Ouellette, FCCP, comments: As a young physician, I learned to divide my patients with pneumonia into two categories, those with "typical" and those with "atypical" pneumonia. I was taught that different pathogens were the etiology for these two different syndromes, and that I should tailor my antimicrobial treatment appropriately. Later, I learned that our clinical acumen was insufficient to distinguish causative agents in patients with pneumonia.



I therefore now teach residents to partition their pneumonia patients into different demographic categories, such as "community-acquired pneumonia" (CAP) and "health care–associated pneumonia." Each category is associated with an evidence-based menu of appropriate antimicrobial strategies.

Results from a new German study suggest that, if clinicians know that they are treating CAP due to *Haemophilus influenza*, outcomes are improved if fluoroquinolones are administered. I wonder, however, how I could be certain early in the clinical course that my patient has pneumonia due to "H Flu"? Do the results apply to other pathogens? Considering that antimicrobial resistance patterns are different in different geographical regions, do these results from Germany apply to my practice in Detroit?

More research is needed to answer these questions.

CDC investigates enterovirus D68, paralysis link

BY NASEEM S. MILLER
Frontline Medical News

Acute onset of limb weakness and an MRI showing a spinal cord lesion largely restricted to the gray matter have been noted in several children who tested positive for enterovirus D68 infections, which have been spreading across the nation.

Federal health officials are urging that cases be reported to state and local health departments. The Centers for Disease Control and Prevention issued the alert in late September in response to an ongoing investigation in Colorado involving nine children who have been hospitalized with acute neurologic illness. A 10th case was later added to the cluster, according to the Colorado Department of Public Health & Environment.

Four of the children have tested positive for the virus, and test results are pending in two other cases. Most cases had a febrile respiratory illness in the 2 weeks before onset of neurologic symptoms.

EV-D68 is a non–polio enterovirus causing mild to severe respiratory illness. Since initial reports in mid-August, more than 440 cases of EV-D68 have been confirmed in 40 states and the District of Columbia. The numbers are likely to increase as states process the backlog of specimens, according to the CDC. "As the scale of this year's EV-D68 outbreak is much larger in comparison to the past, we will likely see rare complications of this infection, such as paralysis," Dr. Jana Shaw, an infectious disease specialist at Upstate Golisano Children's Hospital in Syracuse, N.Y., wrote in an e-mail.

The Colorado cases were identified between Aug. 9 and Sept. 17 this year among children aged 1-18 years, median age 10 years. All were hospitalized. Eight of the nine children are up to date with their polio vaccinations. Most presented with acute focal limb weakness and MRIs showed nonenhancing lesions largely restricted to the gray matter. Some patients had acute cranial nerve dysfunction with correlating nonenhancing brainstem lesions on MRI. There were no cases of altered mental status or seizure, nor any cortical, subcortical, basal ganglia, or thalamic lesions on MRI, the CDC reported.

Nearly half of the specimens tested for EV-D68 at the CDC have tested positive and one-third have tested positive for an enterovirus or rhinovirus other than EV-D68, the agency noted.

"Not much is known about the spectrum and the severity of the disease [EV-D68]," Dr. Shaw said. "Recent reports of polio-like illness among children alert us to include EV-D68 virus in a differential diagnosis when evaluating a pediatric patient with acute focal limb weakness and prior respiratory illness.

In a recent commentary in JAMA Pediatrics, Dr. Shaw wrote that "rapid detection and media collaboration are crucial in limiting the effect of an outbreak in a community."

Health officials in New Jersey confirmed on Oct. 5 the first death attributed directly to EV-D68. A 4-year-old-boy, who had had pinkeye as his only symptom of the virus, died on Sept. 23.

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IOM calls for pay for end-of-life planning

BY ALICIA AULT
Frontline Medical News

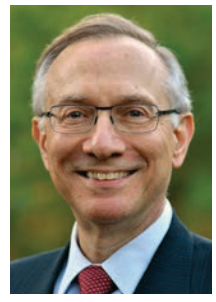
Physicians should be compensated for counseling patients on end-of-life planning, according to recommendations from the Institute of Medicine, and the health care delivery and payment system should be realigned to encourage and financially reward higher-quality, more comprehensive, more efficient, and more humane care for those with serious illnesses.

"Individuals should have time with their doctors to talk about end-of-life issues, and clinicians should receive the training and financial incentives for such discussions," said David Walker, former comptroller general of the United States and cochair of the IOM committee that created the report.

Dying in America calls on health care providers, payers, policy makers, and the American public to have a more open discourse about death and dying.

End-of-life care was caught up in a political firestorm in 2009 when the Obama administration proposed to pay for advanced care conversations under the Affordable Care Act, Dr. Harvey Fineberg, former IOM president, noted in a video message at a briefing. Such efforts were construed as "death panels," and the administration withdrew its proposal within days of its going into effect in 2011, said Dr. Fineberg, now at the University of California, San Francisco.

The report focuses on how individuals and their families can take control of their health, what clinicians and other professionals can do, and what policy makers and payers need to do. The 21-member IOM committee spent 2 years developing the consensus report, Mr. Walker said.


DR. FINEBERG

"For most people, death does not come suddenly," said Dr. Philip Pizzo, committee cochair. "Instead, dying is a result of one or more diseases that must be managed carefully and compassionately over weeks, months, or even years, through many ups and downs," said Dr. Pizzo of Stanford (Calif.) University.

The committee made five broad recommendations:

- Comprehensive care for patients with advanced, serious illness who are nearing the end of life should be covered by public and private payers.
- Evidence-based standards for clinician-patient communication and advanced care planning should be developed by professional societies; such standards should be used as measures for payment, licensing, and credentialing.
- Standardized training and requirements should be developed and implemented.
- Care standards should seek to avoid unnecessary emergency department or acute care services; care should be coordinated across settings and providers by using tools such as interoperable electronic health records and physician orders for life-sustaining treatment programs.
- Fact-based information should be developed and disseminated broadly through public health and other governmental agencies, community-based organizations, and faith-based organizations, as well as through health care providers and payers.

More needs to be done to educate health care providers and patients about the differences between hospice and palliative care, and the potential they have for improving quality of life and reducing unnecessary – and costly – medical services, according to the committee report.

Dr. Pizzo noted that many physicians, when surveyed, have said that they would prefer less-aggressive care at the end of life and having the patient receive care at home. Yet, for their patients, they tend to pull out the stops. He said that was driven by a lack of understanding of individual needs and preferences, and by what he and the committee called the "perverse incentives" of the health care system.

The system rewards more care, not less, and acute care more so than palliative or supportive care, Mr. Walker noted. "Our current system is broken. It does not result in the honoring of individual preferences as much as it should."

The IOM report was financed by an anonymous donor.

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VIEW ON THE NEWS

Dr. Paul A. Selecky, FCCP, comments: This recommendation for end-of-life discussions is long overdue. Physicians have been providing these services for years, and it is appropriate that they be encouraged to provide such care both in and out of the hospital. The impact can be significant for this time-consuming and emotion-consuming practice. Referrals to palliative care will likely increase, as will patient satisfaction scores. Use of hospital resources and their cost are likely to decrease as patients and their families request that nonessential treatment be decreased or stopped. Only good can come from this, once the process has been fully developed by the CMS.

Another chance at meaningful use hardship relief

BY MARY ELLEN SCHNEIDER
Frontline Medical News

Doctors and hospitals are getting another chance to apply for relief from the federal electronic health record meaningful use program and avoid penalties, officials at the Centers for Medicare & Medicaid Services announced.

The agency is reopening the application period for hardship exemptions, specifically for physicians and hospitals that are attesting to their meaningful use of electronic health records (EHRs) for the first time, and who have been using older technology.

The new deadline for hardship applications is 11:59 p.m. EST on Nov. 30.

The deadline to apply for a hardship exemption originally closed on April 1 for hospitals and July 1 for physicians. But the Centers for Medicare & Medicaid Services (CMS) reopened the process after it became clear that a subset of physicians who were attesting to meaningful use for the first time could see a 1% penalty due to a government website problem.

At the center of the problem is a backlog in the availability of newly certified EHR products. Knowing that many physicians and hospitals would be unable to attest to using newly certified products in time for this year's meaningful use deadline, the CMS proposed in May to allow them to attest to using older technology during 2014.

The final rule, released in August, gives physicians the flexibility to use either a 2011 certified product, a newer 2014 certified product, or a combination of both, without being penalized. But the website where physicians must apply for the flexibility was not ready in time for the Oct. 1 attestation deadline.

The mismatch in deadlines raised the ire of physician groups and members of Congress, who called on the CMS to find some pathway for physicians to avoid penalties earned through no fault of their own.

On Oct. 7, the CMS announced that it would reopen the hardship application period for physicians and hospitals that had been unable to fully implement 2014 certified EHRs due to delays in their availability, as well as those who were unable to attest to meaningful use by the deadline and were using the flexibility options outlined by the CMS.

The announcement was praised by the American Medical Association. AMA President Robert M. Wah said the change will allow more physicians to avoid an "unfair" penalty in 2015.

Changes and stages

In August, the CMS officially extended Stage 2 of the program through 2016 for providers who were early adopters – that is, they attested to meaningful use in 2011 or 2012. Stage 3 of the meaningful use program will begin in 2017 for these providers, giving them an additional year to meet the more advanced requirements.

The rule also gave physicians more time to attest to using older technology. Physicians can use the 2011 Edition Certified Electronic Health Record (EHR) Technology or a combination of 2011 and 2014 Edition certified products for the reporting period in 2014. All providers will be required to use 2014 Edition certified products beginning in 2015.

Even with the increased flexibility to use older certified products, physicians will be able to attest for only Stage 1 until they have full access to 2014 Edition certified technology.

Pathogenic bacteria up RSV severity, ICU stay

BY WHITNEY MCKNIGHT
Frontline Medical News

WASHINGTON – Potentially pathogenic nasopharyngeal bacterial colonization was associated with more severe respiratory syncytial virus–related bronchiolitis in infants, according to a study.

"We found that [colonization] was significantly more common and almost double in the RSV patients, compared with controls," said Dr.

VIEW ON THE NEWS

Dr. Burt Lesnick, FCCP, comments: This article highlights an observed association between severe RSV and colonization by pathogenic bacteria. Further investigations into this subgroup of RSV patients for aberrations in their innate immunity would be interesting.

The article does *not* suggest that treatment of the bacteria would positively impact the clinical outcome of the affected patients.

Eleanora Bunsow, a researcher at Nationwide Children's Hospital in Columbus, Ohio, who presented the data at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy. "And RSV patients were frequently colonized with more than one pathogenic bacteria."

Additionally, the use of polymerase chain reaction (PCR) assays to assess bacterial colonization types and levels was found to outperform the accuracy of cultures.

"The PCR showed an increased capacity for bacteria detection and had the ability to quantitate the bacterial load in infant RSV bronchiolitis," Dr. Bunsow said.

While the majority of infants hospitalized with RSV bronchiolitis are previously healthy with no known risk factors, about 15% will require intensive care. The role of pathogenic bacteria has, until recently, been explored only in animal studies, Dr. Bunsow said.

From December 2010 to May 2012, 294 children (median age, 2.5 years) were enrolled at a single site. Of these, 47 were age-matched healthy controls, 182 were inpatient, and 65 were admitted to the ICU. Both inpatient and ICU admissions tended to include twice as many boys as girls (1.6:1 and 1.7:1, respectively). A total of 47% of the control group were African Americans.

Cultures and PCR assays were performed on all study participants for the detection of gram-positive *Staphylococcus aureus* and *Streptococcus pneumoniae*, and gram-negative *Moraxella catarrhalis* and *Haemophilus influenzae*.

PCR had a 1.4-fold higher level of sensitivity (95% confidence interval, 91%-98%) and equal specificity when compared with cultures for identifying all four bacteria tested.

Polymicrobial bacterial colonization

Continued on following page

Continued from previous page

of both gram-positive and gram-negative species was found in 13% of RSV patients, compared with no potentially pathogenic bacterial colonizations in the control group ($P = .004$).

Rates of colonization were also significantly higher in those with severe RSV infections of the lower respiratory tract who were admitted to the pediatric ICU (PICU), compared with inpatients with less severe disease (53.8% vs. 39%). The median clinical disease severity score for those with potentially pathogenic bacterial colonization was 5, compared with a median score of 4 in those without colonization ($P = .187$).

Colonization with gram-negative bacteria was associated with a "significantly higher" need for up to 3 days of ICU oxygen support, compared with needing only up to 2 days of oxygen for colonization with gram-positive bacteria ($P = .039$), Dr. Bunsow noted.

Also, *H. influenzae* was identified in 54% of PICU patients, compared with 39% of inpatient ones. Higher *H. influenzae* loads correlated with PICU lengths of stay ($P = .03$).

Dr. Bunsow said she had no relevant disclosures.

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Do not administer Letairis to a pregnant female because it may cause fetal harm. Letairis is very likely to produce serious birth defects if used by pregnant female, as this effect has been seen consistently when it is administered to animals *[see Contraindications, Use in Specific Populations]*.

Exclude pregnancy before the initiation of treatment with Letairis. Females of Reproductive Potential must use acceptable methods of contraception during treatment with Letairis and for one month after treatment. Obtain monthly pregnancy tests during treatment and 1 month after discontinuation of treatment *[see Use in Special Populations]*.

Because of the risk of embryo-fetal toxicity, females can only receive Letairis through a restricted program called the Letairis REMS Program *[see Warnings and Precautions]*.

INDICATIONS AND USAGE: Letairis is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and delay clinical worsening. Studies establishing effectiveness included predominantly patients with WHO Functional Class II-III symptoms and etiologies of idiopathic or heritable PAH (64%) or PAH associated with connective tissue diseases (32%).

DOSAGE AND ADMINISTRATION: Adult Dosage: Initiate treatment at 5 mg once daily, and consider increasing the dose to 10 mg once daily if 5 mg is tolerated. Tablets may be administered with or without food. Tablets should not be split, crushed, or chewed. Doses higher than 10 mg once daily have not been studied in patients with pulmonary arterial hypertension (PAH). **Pregnancy Testing in Females of Reproductive Potential:** Initiate treatment with Letairis in Females of Reproductive Potential only after a negative pregnancy test. Obtain monthly tests during treatment *[see Use in Specific Populations]*.

CONTRAINDICATIONS: Pregnancy: Letairis may cause fetal harm when administered to a pregnant female. Letairis was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Warnings and Precautions, Use in Specific Populations]*. **Idiopathic Pulmonary Fibrosis:** Letairis is contraindicated in patients with Idiopathic Pulmonary Fibrosis (IPF) including IPF patients with pulmonary hypertension (WHO Group 3) *[see Clinical Studies]*.

WARNINGS AND PRECAUTIONS: Letairis REMS Program: For all females, Letairis is available only through a restricted program called the Letairis REMS, because of risk of embryo-fetal toxicity *[see Contraindications, Warnings and Precautions, Use in Specific Populations]*. Notable requirements of the Letairis REMS Program include that the Prescribers must be certified with the program by enrolling and completing training. All females, regardless of reproductive potential, must enroll in the Letairis REMS Program prior to initiating Letairis. 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]*. Pharmacies that dispense Letairis must be certified with the program and must dispense to female patients who are authorized to receive Letairis. Further information is available at www.letairisrems.com or 1-866-664-5327. **Fluid Retention:** Peripheral edema is a known class effect of endothelin receptor antagonists, and is also a clinical consequence of PAH and worsening PAH. In the placebo controlled studies, there was an increased incidence of peripheral edema in patients treated with doses of 5 or 10 mg Letairis compared to placebo *[see Adverse Reactions]*. Most edema was mild to moderate in severity, and it occurred with greater frequency and severity in elderly patients. In addition, there have been post-marketing reports of fluid retention in patients with pulmonary hypertension, occurring within weeks after starting Letairis. Patients required intervention with a diuretic, fluid management, or, in some cases, hospitalization for decompensating heart failure. If clinically significant fluid retention develops, with or without associated weight gain, further evaluation should be undertaken to determine the cause, such as Letairis or underlying heart failure, and the possible need for specific treatment or discontinuation of Letairis therapy. **Pulmonary Veno-occlusive Disease:** If patients develop acute pulmonary edema during initiation of therapy with vasodilating agents such as Letairis, the possibility of pulmonary veno-occlusive disease should be considered, and if confirmed Letairis should be discontinued. **Decreased Sperm Counts:** Decreased sperm counts have been observed in human and animal studies with another endothelin receptor antagonist and in animal fertility studies with ambrisentan. Letairis may have an adverse effect on spermatogenesis. Counsel patients about potential effects on fertility *[see Specific Populations, Nonclinical Toxicology]*. **Hematological Changes:** Decreases in hemoglobin concentration and hematocrit have followed administration of other endothelin receptor antagonists and were observed in clinical studies with Letairis. These decreases were observed within the first few weeks of treatment with Letairis, and stabilized thereafter. The mean decrease in hemoglobin from baseline to end of treatment for those patients receiving Letairis in the 12 week placebo controlled studies was 0.8 g/dL. Marked decreases in hemoglobin (>15% decrease from baseline resulting in a value below the lower limit of normal) were observed in 7% of all patients receiving Letairis (and 10% of patients receiving 10 mg) compared to 4% of patients receiving placebo. The cause of the decrease in hemoglobin is unknown, but it does not appear to result from hemorrhage or hemolysis. In the long-term open-label extension of the two pivotal clinical studies, mean decreases from baseline (ranging from 0.9 to 1.2 g/dL) in hemoglobin concentrations persisted for up to 4 years of treatment. There have been postmarketing reports of decreases in hemoglobin concentration and hematocrit that have resulted in anemia requiring transfusion. Measure hemoglobin prior to initiation of Letairis, at one month, and periodically thereafter. Initiation of Letairis therapy is not recommended for patients with clinically significant anemia. If a clinically significant decrease in hemoglobin is observed and other causes have been excluded, consider discontinuing Letairis.

ADVERSE REACTIONS: Clinically significant adverse reactions that appear in other sections of the labeling include: Embryo-fetal toxicity *[see Warnings and Precautions, Use in Specific Populations]* Fluid Retention *[see Warnings and Precautions]* Pulmonary Edema with PVOD *[see Warnings and Precautions]* Decreased Sperm Count *[see Warnings and Precautions]* Hematologic changes *[see Warnings and Precautions]*. **Clinical Trials Experience:** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Safety data for Letairis were obtained from two 12 week, placebo controlled studies in patients with pulmonary arterial hypertension (PAH) (ARIES-1 and ARIES-2) and four nonplacebo controlled studies in 483 patients with PAH who were treated with doses of 1, 2.5, 5, or 10 mg once daily. The exposure to Letairis in these studies ranged from 1 day to 4 years (N=418 for at least 6 months and N=343 for at least 1 year). In ARIES-1 and ARIES-2, a total of 261 patients received Letairis at doses of 2.5, 5, or 10 mg once daily and 132 patients received placebo. The adverse reactions that occurred in >3% more patients receiving Letairis than receiving placebo are shown in Table 1.

Table 1 Adverse Reactions with Placebo-Adjusted Rates >3%

	Placebo (N=132)	Letairis (N=261)	
Adverse reaction	**n (%)**	**n (%)**	**Placebo-adjusted (%)**
Peripheral edema	14 (11)	45 (17)	6
Nasal congestion	2 (2)	15 (6)	4
Sinusitis	0 (0)	8 (3)	3
Flushing	1 (1)	10 (4)	3

Most adverse drug reactions were mild to moderate and only nasal congestion was dose dependent. Few notable differences in the incidence of adverse reactions were observed for patients by age or sex. Peripheral edema was similar in younger patients (<65 years) receiving Letairis (14%; 29/205) or placebo (13%; 13/104), and was greater in elderly patients (≥65 years) receiving Letairis (29%; 16/56) compared to placebo (4%; 1/28). The results of such subgroup analyses must be interpreted cautiously. The incidence of treatment discontinuations due to adverse events other than those related to PAH during the clinical trials in patients with PAH was similar for Letairis (2%; 5/261 patients) and placebo (2%; 3/132 patients). The incidence of patients with serious adverse events other than those related to PAH during the clinical trials in patients with PAH was similar for placebo (7%; 9/132 patients) and for Letairis (5%; 13/261 patients). During 12-week controlled clinical trials, the incidence of aminotransferase elevations >3x upper limit of normal (ULN) were 0% on Letairis and 2.3% on placebo. In practice, cases of hepatic injury should be carefully evaluated for cause. Use in Patients with Prior Endothelin Receptor Antagonist (ERA) Related Serum Liver Enzyme Abnormalities: In an uncontrolled, open label study, 36 patients who had previously discontinued endothelin receptor antagonists (ERAs: bosentan, an investigational drug, or both) due to aminotransferase elevations >3x ULN were treated with Letairis. Prior elevations were predominantly moderate, with 64% of the ALT elevations <5x ULN, but 9 patients had elevations >8 x ULN. Eight patients had been re-challenged with bosentan and/or the investigational ERA and all eight had a recurrence of aminotransferase abnormalities that required discontinuation of ERA therapy. All patients had to have normal aminotransferase levels on entry to this study. Twenty-five of the 36 patients were also receiving prostanoid and/or phosphodiesterase type 5 (PDE5) inhibitor therapy. Two patients discontinued early (including one of the patients with a prior 8x ULN elevation). Of the remaining 34 patients, one patient experienced a mild aminotransferase elevation at 12 weeks on Letairis 5 mg that resolved with decreasing the dosage to 2.5 mg, and that did not recur with later escalations to 10 mg. With a median follow-up of 13 months and with 50% of patients increasing the dose of Letairis to 10 mg, no patients were discontinued for aminotransferase elevations. While the uncontrolled study design does not provide information about what would have occurred with re-administration of previously used ERAs or show that Letairis led to fewer aminotransferase elevations than would have been seen with those drugs, the study indicates that Letairis may be tried in patients who have experienced asymptomatic aminotransferase elevations on other ERAs after aminotransferase levels have returned to normal. Postmarketing Experience: The following adverse reactions were identified during postapproval use of Letairis. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to estimate reliably the frequency or to establish a causal relationship to drug exposure: anemia *[see Warnings and Precautions]*, fluid retention *[see Warnings and Precautions]*, heart failure (associated with fluid retention), hypersensitivity (e.g., angioedema, rash), nausea, and vomiting. Elevations of liver aminotransferases (ALT, AST) have been reported with Letairis use; in most cases alternative causes of the liver injury could be identified (heart failure, hepatic congestion, hepatitis, alcohol use, hepatotoxic medications). Other endothelin receptor antagonists have been associated with elevations of aminotransferases, hepatotoxicity, and cases of liver failure *[see Adverse Reactions]*.

DRUG INTERACTIONS: Multiple dose co-administration of ambrisentan and cyclosporine resulted in an approximately 2-fold increase in ambrisentan exposure in healthy volunteers; therefore, limit the dose of ambrisentan to 5 mg once daily when co-administered with cyclosporine *[see Clinical Pharmacology]*.

USE IN SPECIFIC POPULATIONS: Pregnancy Category X: Risk Summary: Letairis may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. Letairis was teratogenic in rats and rabbits at doses which resulted in exposures of 3.5 and 1.7 times respectively the human dose of 10 mg per day. 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, Warnings and Precautions]*. Animal Data: Letairis was teratogenic at oral doses of ≥15 mg/kg/day (AUC 51.7 h•µg/mL) in rats and ≥7 mg/kg/day (24.7 h•µg/mL) in rabbits; it was not studied at lower doses. These doses are of 3.5 and 1.7 times respectively the human dose of 10 mg per day (14.8 h•µg/mL) based on AUC. In both species, there were abnormalities of the lower jaw and hard and soft palate, malformation of the heart and great vessels, and failure of formation of the thymus and thyroid. A preclinical study in rats has shown decreased survival of newborn pups (mid and high doses) and effects on testicle size and fertility of pups (high dose) following maternal treatment with ambrisentan from late gestation through weaning. Doses tested were 17x, 51x, and 170x (on a mg/kg:mg/m^2 basis) the maximum oral human dose of 10 mg and an average adult body weight of 70 kg.

Nursing Mothers: It is not known whether ambrisentan is present in human milk. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from Letairis, a decision should be made whether to discontinue nursing or discontinue Letairis, taking into account the importance of the drug to the mother. **Pediatric Use:** Safety and effectiveness of Letairis in pediatric patients have not been established. **Geriatric Use:** In the two placebo controlled clinical studies of Letairis, 21% of patients were ≥65 years old and 5% were ≥75 years old. The elderly (age ≥65 years) showed less improvement in walk distances with Letairis than younger patients did, but the results of such subgroup analyses must be interpreted cautiously. Peripheral edema was more common in the elderly than in younger patients. **Females and Males of Reproductive Potential:** Pregnancy Testing: Female patients of reproductive potential must have a negative pregnancy test prior to initiation of treatment, monthly pregnancy test during treatment, and 1 month after stopping treatment with Letairis. Advise patients to contact their health care provider if they become pregnant or suspect they may be pregnant. Perform a pregnancy test if pregnancy is suspected for any reason. For positive pregnancy tests, counsel patient on the potential risk to the fetus and patient options *[see Boxed*

Prenatal BPA exposure linked to adverse lung effects

BY AMY KARON
Frontline Medical News

Early prenatal exposure to bisphenol A was linked to diminished lung function at age 4 years and to persistent childhood wheezing, according to a birth cohort analysis reported online in JAMA Pediatrics.

In the study, which enrolled 398 pairs of English-speaking mothers and infants in the Cincinnati area, every 10-fold increase in maternal urinary concentration of BPA at 16 weeks' gestation led to a 4.27-fold rise in the odds of persistent wheezing in offspring, the researchers reported. The findings "confirm and extend" the results for parent-reported wheezing from the same cohort at age 3 years, said Dr. Adam J. Spanier of the University of Maryland in Baltimore and his associates (JAMA Pediatr. 2014 Oct. 6 [doi:10.1001/jamapediatrics.2014.1397]). There also was an association of increasing mean maternal urinary BPA level with decreasing percent predicted forced expiratory volume at age 4 years. However, the effect on lung function was not seen for children aged 5 years.

The authors reported having no relevant financial conflicts.

Warning and Dosage and Administration]. Contraception: Female patients of reproductive potential must use acceptable methods of contraception during treatment with Letairis and for 1 month after stopping treatment with Letairis. Patients may choose one highly effective form of contraception (intrauterine devices (IUD), contraceptive implants, or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a partner's vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider trained in contraceptive counseling *[see Boxed Warning]*. Infertility: Males In a 6-month study of another endothelin receptor antagonist, bosentan, 25 male patients with WHO functional class III and IV PAH and normal baseline sperm count were evaluated for effects on testicular function. There was a decline in sperm count of at least 50% in 25% of the patients after 3 or 6 months of treatment with bosentan. One patient developed marked oligospermia at 3 months and the sperm count remained low with 2 follow-up measurements over the subsequent 6 weeks. Bosentan was discontinued and after 2 months the sperm count had returned to baseline levels. In 22 patients who completed 6 months of treatment, sperm count remained within the normal range and no changes in sperm morphology, sperm motility, or hormone levels were observed. Based on these findings and preclinical data *[see Nonclinical Toxicology]* from endothelin receptor antagonists, it cannot be excluded that endothelin receptor antagonists such as Letairis have an adverse effect on spermatogenesis. Counsel patients about the potential effects on fertility *[see Warnings and Precautions]*. **Renal Impairment:** The impact of renal impairment on the pharmacokinetics of ambrisentan has been examined using a population pharmacokinetic approach in PAH patients with creatinine clearances ranging between 20 and 150 mL/min. There was no significant impact of mild or moderate renal impairment on exposure to ambrisentan *[see Clinical Pharmacology]*. Dose adjustment of Letairis in patients with mild or moderate renal impairment is therefore not required. There is no information on the exposure to ambrisentan in patients with severe renal impairment. The impact of hemodialysis on the disposition of ambrisentan has not been investigated. **Hepatic Impairment: Pre-existing hepatic impairment:** The influence of pre-existing hepatic impairment on the pharmacokinetics of ambrisentan has not been evaluated. Because there is *in vitro* and *in vivo* evidence of significant metabolic and biliary contribution to the elimination of ambrisentan, hepatic impairment would be expected to have significant effects on the pharmacokinetics of ambrisentan *[see Clinical Pharmacology]*. Letairis is not recommended in patients with moderate or severe hepatic impairment. There is no information on the use of Letairis in patients with mild pre-existing impaired liver function; however, exposure to ambrisentan may be increased in these patients. **Elevation of Liver Transaminases:** Other endothelin receptor antagonists (ERAs) have been associated with aminotransferase (AST, ALT) elevations, hepatotoxicity, and cases of liver failure *[see Adverse Reactions]*. In patients who develop hepatic impairment after Letairis initiation, the cause of liver injury should be fully investigated. Discontinue Letairis if aminotransferase elevations >5x ULN or if elevations are accompanied by bilirubin >2x ULN, or by signs or symptoms of liver dysfunction and other causes are excluded.

OVERDOSAGE: There is no experience with overdosage of Letairis. The highest single dose of Letairis administered to healthy volunteers was 100 mg and the highest daily dose administered to patients with PAH was 10 mg once daily. In healthy volunteers, single doses of 50 mg and 100 mg (5 to 10 times the maximum recommended dose) were associated with headache, flushing, dizziness, nausea, and nasal congestion. Massive overdosage could potentially result in hypotension that may require intervention.

PATIENT COUNSELING INFORMATION: *See FDA-approved patient labeling (Medication Guide).* **Embryo-fetal toxicity:** Instruct patients on the risk of fetal harm when Letairis is used in pregnancy *[see Warnings and Precautions; Use in Special Populations]*. Female patients must enroll in the Letairis REMS Program. Instruct Females of Reproductive Potential to immediately contact their physician if they suspect they may be pregnant. **Letairis REMS Program:** For female patients, Letairis is only available through a restricted program called the Letairis REMS *[see Contraindications, Warnings and Precautions]*. Male patients are not enrolled in the Letairis REMS. Inform female patients (and their guardians, if applicable) of the following notable requirements: All female patients must sign an enrollment form. Advise female patients of reproductive potential that they must comply with the pregnancy testing and contraception requirements *[see Use in Specific Populations]*. Educate and counsel Females of Reproductive Potential on the use of emergency contraception in the event of unprotected sex or known or suspected contraceptive failure. Advise pre-pubertal females to report any changes in their reproductive status immediately to their prescriber. Review the Letairis Medication Guide and REMS educational material with female patients. A limited number of pharmacies are certified to dispense Letairis. Therefore, provide patients with the telephone number and website for information on how to obtain the product. **Hepatic Effects:** Some members of this pharmacological class are hepatotoxic. Patients should be educated on the symptoms of potential liver injury (such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant abdominal discomfort, jaundice, dark urine or itching) and instructed to report any of these symptoms to their physician. **Hematological Change:** Patients should be advised of the importance of hemoglobin testing. **Administration:** Patients should be advised not to split, crush, or chew tablets.

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Fur bedding lowered asthma risk, but raises SIDS concern

BY AMY KARON
Frontline Medical News

Babies who slept on animal skins during their first 3 months of life were almost 40% less likely to have asthma by the time they were 10 years old, according to a population-based cohort study.

Sleeping on animal skins during infancy also was linked to lower odds of wheezing and hay fever, but did not seem to affect eczema or sensitivity to airborne antigens, Dr. Christina Tischer reported at the annual meeting of the European Respiratory Society.

"Early exposure to animal fur could be a simple, cheap, and effective way to resemble an environment with higher microbial exposure," said Dr. Tischer, a researcher at the German Institute for Environmental Health in Neuherberg. "It might follow similar protective mechanisms in relation to asthma and allergy as it has been observed in farm and rural environments."

The investigators studied 2,441 children in Germany who were up to 10 years old; parents answered a series of questionnaires about asthma and respiratory risk factors and health outcomes. In all, 55% of the children slept on animal skins or animal furs during their first 3 months of life, Dr. Tischer and her associates reported.

By age 10 years, children who slept on animal skins or animal fur as infants had a 25% lower odds of ever having wheezed (adjusted odds ratio, 0.75), a 38% lower odds of having been diagnosed with asthma (aOR, 0.62), and a 35% lower odds of having been diagnosed with hay fever (aOR, 0.65) compared with children who did not sleep on animals skins or furs as infants, the investigators reported.

Funding information for the study was not available. Dr. Tischer reported no conflicts of interest.

VIEW ON THE NEWS

Dr. Susan Millard, FCCP, comments: Sleeping on animal skins or fur in the first 3 months of life may decrease the risk of childhood atopy BUT increases the risk of death related to Sudden Infant Death Syndrome (SIDS). This study is from Germany, which may explain cultural differences regarding bedding for infants, but there are reports of cultural diversity regarding bedding for infants even in the United States.

The journal Pediatrics published a study looking at data in 2011 discussing African American parental decisions about infant bedding and sleep surfaces (Pediatrics 2011;128;494). The American Academy of Pediatrics (AAP) supports the policy that infants should sleep on firm bedding. Specifically, infants should not be placed on soft bedding, including blankets, pillows, or sheepskin, for example. In addition, crib bumpers should not be used. Finally, once the AAP promoted the "Back to Sleep" program (meaning babies should NOT be placed on their tummies to sleep), SIDS deaths in the United States decreased.

PALLIATIVELY SPEAKING Reflections on being a patient

BY DR. LEIGH A. FREDHOLM

Recently, I had an unexpected hospitalization for what ultimately proved to be ovarian torsion. I spent 4 nights in the hospital, 2 preoperatively and 2 postoperatively. While I was pleased with the care I received, I also learned a few things that will influence my future hospital-based practice. Herewith, in no particular order, are my observations:

▸ **Emergency department wait times matter.** Much has been written about inappropriate utilization of the ED and throughput. I realize that not everyone in the waiting room has a truly emergent problem, but the 75 minutes between my arrival and the time I was triaged were the longest 75 minutes of my life. I was in so much pain that I couldn't even advocate for myself.

▸ **When faced with equivocal diagnostic testing, return to the history and physical** as Sir William Osler instructed. ("Listen to your patient; he is telling you the diagnosis.") I am so fortunate to live in the 21st century and to have immediate access to diagnostic imaging, labs, and a good surgeon. It is not lost on me, however, had that CT and ultrasound not been available (and nondiagnostic), my exam and white blood cell count would have taken me to the operating room without delay, shortening both my hospital stay and my recovery time. Still, I recognize that the retrospectoscope has 100% accuracy, far exceeding that of we human physicians.

▸ **Opioids are not the enemy.** After receiving multiple doses of intravenous opioids in the ED, I asked for ketorolac. During the 2 days between onset of pain and surgery, I relied upon the ketorolac for most of my pain relief. This is in part because I felt it worked better than the opioids (but did not eliminate the need for opioids) but also in an effort to be a "good patient." When

VIEW ON THE NEWS

Dr. Paul A. Selecky, FCCP, comments: It is often enlightening to be on the receiving end of the stethoscope and thus learn more about how we care for our patients. It brings to mind the oft-quoted phrases from Francis Peabody's lectures to Harvard medical students published in JAMA (1927;88:877-82), in which he said, "Time, sympathy and understanding must be lavishly dispensed, for the reward is to be found in that personal bond which forms the greatest satisfaction of the practice of medicine. One of the essential qualities of the clinician is interest in humanity, for the secret of the care of the patient is in caring for the patient."

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I thought I might be going home, I stopped asking for the ketorolac. In short order, the pain worsened, my vital signs worsened, and I was off to the OR for removal of what proved to be a hemorrhagic, necrotic ovary.

▸ **Small things matter, communication.** Our system has spent considerable energy improving communication between staff and patients, utilizing communication boards. The professionals caring for me performed wonderfully in this respect – without fail, I knew their names and their extensions. I never knew, though, when my doctor would be rounding.

Because of on-call responsibilities and emergencies, the times ranged between 6 a.m. and 2 p.m. I completely understand why this happens, as it has occurred in my own practice. I will remember to keep my patients informed about my own schedule as much as I can going forward.

▸ **Small things matter, miscellaneous.** Medical tape leaves adhesive residue that takes days to remove. … Nail polish remover is more effective than alcohol for adhesive removal. … An improperly secured Foley catheter can wreak havoc. … There is literally nothing on TV worth watching for days at a time, despite having 46 channels. … Clear liquids have more sugar than should be allowed, even for those of us who are not diabetic.

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▸ **Being sick is very tedious.**

As a medical student (more years ago than I care to count), I participated in various activities intended to raise awareness and sensitivity to the patient experience. After my recent refresher course, I hope to be a better doctor to my patients.

Dr. Fredholm and her colleague Dr. Stephen Bekanich are codirectors of Seton Palliative Care, part of the University of Texas Southwest Residency Programs in Austin. They alternate contributions to the Palliatively Speaking blog (http://tinyurl.com/Palliatively).

To identify the symptoms of narcolepsy,

LOOK DEEPER

C **Cataplexy:** A sudden, temporary loss of muscle tone triggered by strong emotions[1,2]

H **Hypnagogic Hallucinations:** Vivid dream-like experiences that occur during the transitions between wake and sleep[1,2]

E **Excessive Daytime Sleepiness:** The inability to stay awake and alert during the day, resulting in unintended lapses into drowsiness or sleep[2]

S **Sleep Paralysis:** The temporary inability to move or speak while falling asleep or waking up[2]

S **Sleep Disruption:** The interruption of sleep by frequent awakenings[1,2]

C.H.E.S.S. is a useful mnemonic for recalling the 5 symptoms of narcolepsy,[3] although not all patients experience all symptoms.[2] Narcolepsy is primarily characterized by excessive daytime sleepiness and cataplexy.[2] All patients with narcolepsy have excessive daytime sleepiness.[2] The presence of cataplexy is pathognomonic for narcolepsy.[2]

Narcolepsy Is a Chronic, Life-Disrupting Neurologic Disorder[2,3]
Narcolepsy is a chronic, life-disrupting neurologic disorder in which the brain is unable to regulate sleep-wake cycles normally, resulting in sleep-wake state instability.[1-4]

Narcolepsy Is Underdiagnosed
It is estimated that approximately 50% or more of individuals with narcolepsy remain undiagnosed.[1] Initial onset of symptoms typically occurs between the ages of 15-25,[2] although an accurate diagnosis can take more than 10 years.[1]

Narcolepsy Symptoms Can Be Difficult to Recognize
Narcolepsy symptoms may overlap with those of other conditions, such as obstructive sleep apnea and depression.[1,2] The initial and presenting symptom is typically some manifestation of excessive daytime sleepiness such as tiredness, fatigue, difficulty concentrating, or mood changes.[1,2,5] Individual symptoms should be evaluated carefully to determine whether they are due to narcolepsy or another condition. Looking deeper at the symptoms can help healthcare professionals establish a differential diagnosis.

Get a Deeper Look, at www.NarcolepsyLink.com

Narcolepsy Link contains resources to help identify narcolepsy symptoms and facilitate communications with your patients.

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CRITICAL CARE COMMENTARY ARDS: The past, present, and future

ARDS *from page 1*

mechanical ventilation have evolved and now provide options for support of the patient with ARDS.

ARDS is characterized by Po_2/Fio_2 greater than 300, bilateral radiographic opacities not fully explained by effusions, collapse, or nodules, and respiratory failure not fully explained by cardiac failure or fluid overload (ARDS Definition Taskforce. *JAMA*. 2012;307[23]:2526). Alveoli are filled with edema fluid, inflammatory cells, debris, and cytokines with failure of surfactant to prevent loss of alveolar airspace and collapse. Overall lung compliance is reduced. Airspace heterogeneity, as well as the normal gravitational pleural pressure gradient, contributes to the variability of injured alveoli to reopen and remain inflated in response to increases in airway pressure and lung volume. The low ventilation/perfusion ratio results in shunt physiology with hypoxemia refractory to increasing Fio_2.

Classic ventilatory support

Up until the past 2 decades, gas exchange in ARDS conventionally was supported with use of high Fio_2, high tidal volumes with high end-inspiratory pressures, and high levels of positive end-expiratory pressure.

EDITOR'S COMMENT

In this very thorough review, Dr. Warshawsky has highlighted the over 50-year history of ARDS. Recognition of ARDS has improved with unified criteria, and protective lung strategies have shown significant survival benefit. Until recently, morbidity was not really looked at. Now with a more thorough understanding of post-ARDS complications, ie, PTSD and cognitive and physical impairments, survival is not the only important metric. As prior commentaries have discussed less sedation, early mobilization, and implementing standardized best practice, we hope to improve some of these secondary issues.

The future is better but as new modalities evolve, early adaption may not yield the benefit we expect. As we have seen with ECMO and prone ventilation, whose first iterations were not successful, their overall utility may still evolve with further refinement.

Dr. Peter Spiro, FCCP, Section Editor

Gas exchange could be achieved but without improvement in mortality and morbidity. Over-distension of intact, more compliant alveoli, and shear stress from injured alveoli repetitively opening and collapsing during each ventilatory cycle occur. Airway rupture results in pneumothorax, pneumomediastinum, subcutaneous emphysema, or air embolism. Cytokines that potentiate ongoing diffuse alveolar damage (as well as systemic effects) are liberated. Frequency of distention and rate of distension of the lung also contribute to inflammation (MacIntyre. *Clin Chest Med*. 29[2];2008:225). Increased pressure in the airway and pleura is transmitted to the mediastinum and contributes to impaired cardiac filling and cardiac output (Lansdorp et al. *Crit Care Med*. 2014;42[9]:1983).

Lung protective ventilation

The goal of treatment is to achieve essential physiologic targets while avoiding iatrogenic lung injury. These targets are to maintain perfusion and ventilation of alveoli capable of gas exchange and maintain cardiac output for organ perfusion and oxygen delivery. Fio_2 less than 60% avoids lung inflammation and injury associated with extended exposure to higher Fio_2. The lowest Fio_2 that achieves arterial Po_2 greater than 55 mm Hg, hemoglobin oxygen saturation in the range of 88 to 95%, and arterial pH greater than 7.15 to 7.20 is sufficient. Avoid injury to healthy, functional, compliant alveoli by overdistension. Injured, but potentially functional collapsed alveoli should open during inspiration and maintain inflation during expiration.

Studies have indicated improved survival among patients treated with lower tidal volumes. In a landmark study, the researchers of the ARDS Clinical Trials Network (ARDSNET, *N Engl J Med*. 2000;342[18]:1301) demonstrated improved survival despite worse, yet tolerable gas exchange compared with use of "conventional" ventilation strategies. The collaborative studied tidal volumes of 6 mL/kg to as low as 4 mL/kg ideal body weight, while limiting inspiratory plateau pressures to 30 cm H_2O, as long as tolerable gas exchange and acid/base targets were met. Tolerance of these ventilation parameters was achieved by manipulation of inspiratory flows, respiratory rate, PEEP, Fio_2, and judicious use of sedatives and analgesics. Tidal volume greater than 6 mL/kg was employed

CHEST

Dr. Martin E. Warshawsky, FCCP

when necessary to maintain acceptable alveolar ventilation and pH. This protective strategy is widely accepted for treatment of ARDS. However, one need be cognizant of situations, such as increased intracranial pressure in which the impaired venous return associated with high airway pressures, or the hypoventilation and respiratory acidosis associated with small tidal volumes is deleterious. Such patients were excluded from the ARDSNET trial. Subsequent study of this lung protective ventilation comparing a higher PEEP/lower Fio_2 strategy to the original lower PEEP/higher Fio_2 strategy (Brower et al. *N Engl J Med*. 2004;351[4]:327) showed no difference in mortality or duration of mechanical ventilation.

Alveolar recruitment

Atelectatic lung alveoli, once open, will remain open at lower airway pressures. By taking advantage of this effect of surfactant, lower end-expiratory pressures and volumes are necessary in order to avoid derecruitment. Various types of "recruitment maneuvers" that use periodically increased inspiratory volumes can be applied but are of uncertain benefit. Historically, sigh breaths were used. CPAP of 30 to 45 cm H_2O for 30 to 90 s achieves increased end-expiratory volume, lung distension, and inspiratory pressure. Extending the duration of the inspiratory phase of the ventilatory cycle provides more time for "slower" alveoli to open. Severely injured, collapsed, noncompliant alveoli that require high positive end-expiratory pressure to maintain recruitment are at risk for further injury from repeated opening and closing cycles, and likely incapable of participating in gas exchange (MacIntyre. *Clin Chest Med*. 29[2]; 2008:233). One must observe significant improvement in lung compliance and hemoglobin oxygen saturation in response to recruitment maneuvers and avoid the adverse effects of higher mean airway pressures on venous return, alveolar capillary perfusion, dead space volume, and cardiac output, and barotrauma risk.

Other modes of mechanical ventilation are available that can assist in recruitment of alveoli and limit overdistension of healthier alveolar units. In pressure-cycled ventilation inspiratory and expiratory pressures, inspiratory time, and compliance of lung units determine end-inspiratory volume. Inverse ratio ventilation prolongs inspiratory time to recruit alveoli and prevent subsequent collapse with lower tidal volumes and PEEP. Airway pressure release ventilation is another mode of ventilation that prolongs inspiratory time, allowing for alveolar recruitment with potentially lower tidal volumes and PEEP. It allows the patient to take spontaneous, unsupported breaths and may reduce the need for deep sedation. High frequency ventilation provides for high mean airway pressures for recruitment with reduced tidal volumes and end inspiratory volumes. Despite their beneficial effects on alveolar recruitment and support of gas exchange, these have not been demonstrated to provide superior outcomes to use of low tidal volume strategies. "Prone positioning" has been used to recruit, ventilate, and perfuse alveoli. A study by Guerin et al (*N Engl J Med*. 2013;368[23]:2159) of patients with ARDS and Po_2/Fio_2 less than 150, and at least 5 cm H_2O of PEEP and tidal volume of 6 mL/kg demonstrated that use of 16 hours per day of prone positioning was able to demonstrate improvements in 28-day and 90-day mortality. Prone positioning, even with specialized beds that secure and rotate the patient 180 degrees, is very cumbersome, requires increased resources, increased sedation for patient tolerance, and had to be used early, not as salvage.

Alternative therapies

Extracorporeal membrane oxygenation provides for gas exchange while minimizing or eliminating lung distension and airway opening cycles. It is an effective therapy for patients with severely reduced Po_2/Fio_2 and severely reduced lung compliance. It can provide opportunity for earlier mobilization of the patient with reduced need for sedatives. However, it is associated with a high rate of complications and should only be performed at centers

Continued on following page

Continued from previous page

with appropriate experience and expertise (Brodie et al. *N Engl J Med*. 2011;365[20]:1905).

Inhaled nitric oxide can be used to reduce shunt fraction, shifting the balance of perfusion toward alveoli capable of participating in gas exchange. A recent meta-analysis has failed to demonstrate a survival benefit (Adhikari et al. *Crit Care Med*. 2014;42[2]:404.

Caveats

Lung protective ventilation strategies for ARDS rely on assessments of pulmonary compliance and airway pressures. Patient inspiratory efforts and ventilator dyssynchrony affect airway pressures. Airway pressures reflect not only compliance of lungs but of the entire ventilatory system, including chest wall, and diaphragm and intraabdominal pressure. Edema of chest wall, ascites, and morbid obesity will increase intrathoracic pressures. In such circumstances, airway pressure measurements can be misleading (Slutsky et al. *N Engl J Med*. 2013;369[22]: 2126).

The patient with ARDS benefits from standardized ICU best practices. Minimize edema with attention to fluid balance. Limit metabolic demands by treating SIRS with early goal-directed therapy, and supporting nutrition can reduce ventilatory demand and the work of breathing. A "bundle" of ventilator best practices should be systematically applied to all ventilator patients. This includes head of bed elevation greater than 30 degrees, oral hygiene regimen, titrated sedation/analgesia, routine sedation interruption, daily ventilator weaning readiness assessment, stress ulcer prophylaxis, and deep vein thrombosis prophylaxis. Avoid nosocomial infection by limiting use of indwelling catheters and meticulous practice of hand hygiene.

The benefit of any ARDS ventilation strategy cannot be simply assessed by measurements of survival and ventilator-free days. Outcome is greatly influenced by how reliably the proven adjunctive therapies and ICU best practices protocols are applied. Outcomes need be assessed by measures of long-term survival, ability to preserve cognitive function, and return to an acceptable quality of life. Hospital and long-term care costs for survivors unable to return to their previous level of function are important metrics that only until recently have been ignored.

Dr. Warshawsky is Director of the MICU, Elmhurst Hospital Center; and Clinical Assistant Professor of Medicine, Icahn School of Medicine at Mount Sinai, New York.

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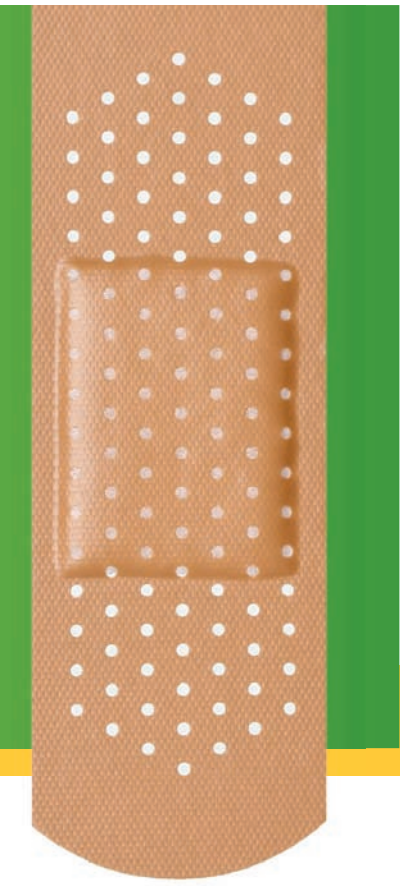

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Benralizumab fails to decrease COPD exacerbations

BY MARY ANN MOON
Frontline Medical News

Benralizumab, a monoclonal antibody to an interleukin-5 receptor that reduces eosinophil counts in the sputum and the blood and has been used to treat asthma, failed to decrease acute exacerbations of chronic obstructive pulmonary disease in an industry-sponsored phase II clinical trial reported at the European Respiratory Society International Congress 2014.

In what they described as the first study of a biologic treatment for eosinophilic COPD, researchers found that benralizumab rapidly depleted both sputum and blood eosinophils "to a much greater extent than did inhaled or oral corticosteroids in other studies," but nonetheless failed to fulfill the primary endpoint of reducing the rate of acute exacerbations, Dr. Christopher E. Brightling said in a paper simultaneously presented at the Congress and published online in Lancet (2014 [doi:10.1016/S2213-2600(14)70187-0]).

During a 3-year period, the double-blind trial enrolled 101 adults aged 45-80 years who were current or past smokers and had moderate to severe COPD. They were treated at 26 medical centers in the United Kingdom, Poland, Germany, Canada, the United States, Denmark, and Spain. These participants were randomly assigned to receive a total of eight subcutaneous injections of 100 mg benralizumab (51 patients) or a matching placebo (50 patients) at intervals over the course of 48 weeks, said Dr. Brightling of the National Institute for Health Research respiratory biomedical research unit, University of Leicester, England.

The primary endpoint, the annualized rate of acute COPD exacerbations at week 56, was 0.95 with benralizumab and 0.92 with placebo, a nonsignificant difference. There also was no significant difference between the two study groups in the need for oral corticosteroids or intravenous antibiotics, nor in the rate of hospitalization.

Benralizumab did deplete blood and sputum eosinophils at the first assessment of these outcomes, an effect that persisted throughout the treatment period and well beyond. It also produced clinically significant improvements in both prebronchodilator and postbronchodilator forced expiratory volume in 1 second, from the first assessment of these outcomes until week 80 – 32 weeks after the final dose was administered.

The benralizumab group had a higher rate of serious adverse events than did the placebo group, but none of those events were considered to be drug related. No hypersensitivity reactions or immune-complex disorders occurred.

This study was funded by MedImmune, maker of benralizumab, which also participated in study design, data analysis, and manuscript preparation. Dr. Brightling reported receiving grants from MedImmune, GlaxoSmithKline, Roche, Novartis, and Chiesi; his associates reported ties to numerous industry sources.

chestphysician@frontlinemedcom.com

VITALS

Key clinical point: Benralizumab was no better than oral steroids or intravenous antibiotics for preventing COPD exacerbations.

Major finding: The annualized rate of acute COPD exacerbations at week 56 was 0.95 with benralizumab and 0.92 with placebo, and there was no significant difference between the two study groups in the need for oral corticosteroids or intravenous antibiotics, nor in the rate of hospitalization.

Data source: A randomized, double-blind international phase II clinical trial involving 101 adults with moderate to severe COPD who received either benralizumab or placebo injections over the course of 48 weeks and were followed for up to 80 weeks.

Disclosures: This study was funded and designed by MedImmune, maker of benralizumab. Dr. Brightling reported receiving grants from MedImmune, GlaxoSmithKline, Roche, Novartis, and Chiesi; his associates reported ties to numerous industry sources.

VIEW ON THE NEWS

Dr. Eric Gartman, FCCP, comments: The utilization of specific targeted therapies is rapidly expanding and holds great promise in pulmonary medicine to improve outcomes while exposing our patients to less systemic side effects. In this case, the anti–IL-5 receptor antibody performed as expected in reducing eosinophilic inflammation, but it was unsuccessful in reducing exacerbation rates, suggesting that if one therapeutic focus exists in this specific population of patients, it may not be solely part of the eosinophilic inflammatory pathway. The biologic factors leading to COPD exacerbations are quite numerous and present a complicated "target," and it may prove difficult to find one drug that fits all patients – and as we learn more about the factors that affect different types of patients, we will be able to tailor therapies to fit a given individual.

Long-term benzo use raises Alzheimer's risk

Benzodiazepine *from page 1*

pines for 180 or more days (adjusted OR, 1.84; 95% CI, 1.62-2.08).

The researchers also found that the type of benzodiazepine prescribed affected risk. Drugs with longer half-life, such as diazepam and clonazepam, were associated with greater likelihood of Alzheimer's disease (OR, 1.70; 95% CI, 1.46-1.98), compared with shorter-acting drugs, such as lorazepam and alprazolam (OR, 1.43; 95% CI, 1.27-1.61). The association between benzodiazepine use and Alzheimer's persisted even after researchers adjusted for symptoms that could be indicative of a future dementia diagnosis, including depression, anxiety, and insomnia (BMJ 2014 Sept. 9 [doi:10.1136/bmj.g5205]).

While the study authors acknowledged that they could not rule out that anxiety and sleep disorders, two of the main indications for benzodiazepines, "could be associated with early beta amyloid lesions in brain, and persistent mid-life anxiety could be associated with a greater risk of dementia in older people," they also noted that their study was designed to reduce the possibility of reverse causation bias "and to provide additional arguments linking benzodiazepine use with Alzheimer's disease, such as a dose-effect relation."

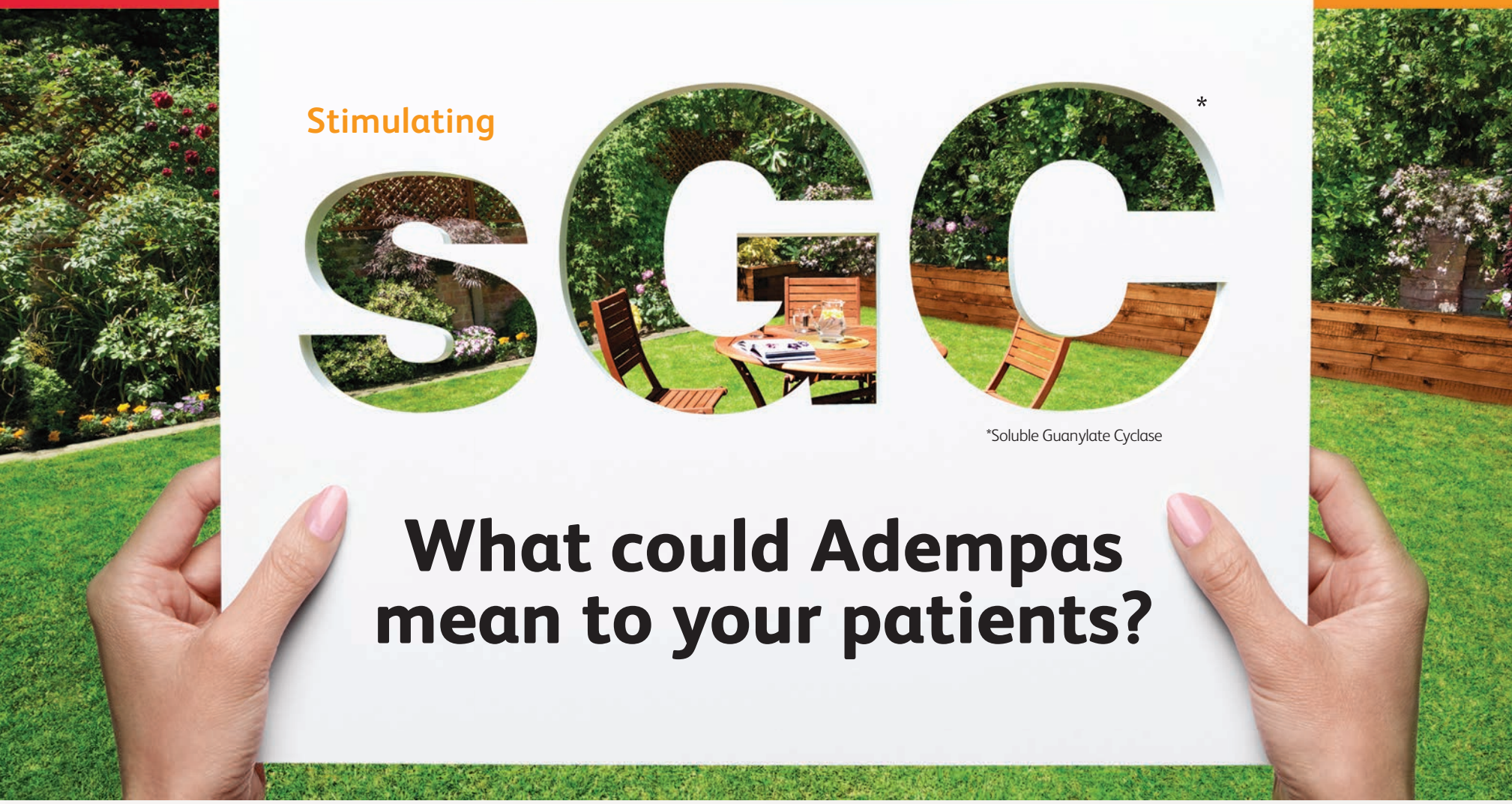
The findings, Ms. Billioti de Gage and her colleagues added, argue for "carefully evaluating the indications for use of this drug class … especially considering the prevalence and chronicity of benzodiazepine use in older people and the high and increasing incidence of dementia in developed countries."

The study was funded by INSERM (Institut National de la Santé et de la Recherche Médicale) and the University of Bordeaux, as well as by unconditional grants from IRESP (Institut de Recherche en Santé Publique), the French Ministry of Health, and the Funding Agency for Health Research of Quebec. One of the study's coauthors, Dr. Tobias Kurth, declared payment from BMJ and Cephalalgia; another co-author, Marie Tournier, declared receiving honoraria from AstraZeneca, Bristol-Myers Squibb, and Janssen.

VIEW ON THE NEWS

Dr. W. Michael Alberts, FCCP, comments: As more and more individuals are living well into their 80s and 90s, we can expect an increase in the burden of neurodegenerative illness including Alzheimer's disease. This study showed that the likelihood of developing Alzheimer's later in life was associated with prolonged exposure to benzodiazepines and to their duration of action. Monitoring cognitive side effects of medications is difficult and proving cause and effect can be challenging. For me, this reiterates the need to complete "medication reconciliation" at each patient encounter. Doing so may prevent duplication from different providers, maintains an up to date medication list, and most importantly, reassesses the need for continuation of medications being prescribed. In addition, before prescribing a medication, carefully consider the potential side effects and long-term consequences.

First and only treatment approved for both **PAH** and inoperable or persistent/recurrent **CTEPH** after surgery†



What could Adempas mean to your patients?

†INDICATIONS

- Adempas (riociguat) tablets are 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.
- 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 predominantly patients with WHO functional class II–III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%).

‡Time to clinical worsening was a combined endpoint defined as death (all-cause mortality), heart/lung transplantation, atrial septostomy, hospitalization due to persistent worsening of pulmonary hypertension, start of new PAH-specific treatment, persistent decrease in 6MWD and persistent worsening of WHO functional class.

IMPORTANT SAFETY INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

Do not administer Adempas (riociguat) tablets 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, Adempas is available only through a restricted program called the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program.

FOR PAH. FOR CTEPH.

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Please see additional Important Safety Information, including Boxed Warning, throughout and Brief Summary of Prescribing Information at end of advertisement.

Adempas could mean moving from the couch to the kitchen

Patients walked farther with Adempas at Week 12: results from Week 2 onward

36m improvement (mean) in 6-minute walk distance (6MWD) over placebo at Week 12 (95% Confidence Interval (CI): 20m-52m; p<0.0001) for PAH (WHO Group 1) patients.

WHO FUNCTIONAL CLASS

50%

more PAH patients improved WHO Functional Class vs placebo (p=0.0033; Adempas: n=53/254 [21%], placebo: n=18/125 [14%]) at Week 12.

Deteriorated

4% for Adempas (n=9/254)

14% for placebo (n=18/125)

Stable

76% for Adempas (n=192/254)

71% for placebo (n=89/125)

PATENT-1: 443 PAH patients were studied. (Adempas 2.5 mg n=254, 1.5 mg n=63, placebo n=126)

Baseline characteristics:

– PAH defined as: pulmonary vascular resistance (PVR) >300 dyn·sec·cm^{-5}, mean pulmonary arterial pressure (mPAP) >25 mm Hg

– Mean age: 51 years (approximately 80% female)

– PAH etiologies: idiopathic (61%), familial (2%), associated with connective tissue disease (25%), congenital heart disease (8%), portal hypertension (3%), or anorexigen or amphetamine use (1%)

– Mean 6MWD was 363m

– Concomitant medications: Oral anticoagulants, diuretics, digitalis, calcium channel blockers, and oxygen were allowed

Patient population was: 50% treatment-naïve, 44% pretreated with an endothelin receptor antagonist (ERA), and 6% pretreated with a prostacyclin analogue (PCA). The majority of patients had WHO Functional Class II (42%) or III (54%) at baseline. Patients with systolic blood pressure <95 mm Hg were excluded.

CONTRAINDICATIONS

Adempas is contraindicated in:

- Pregnancy. Adempas may cause fetal harm when administered to a pregnant woman. 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 while taking this drug, the patient should be apprised of the potential hazard to the fetus
- Co-administration with nitrates or nitric oxide donors (such as amyl nitrite) in any form.
- Concomitant administration with specific phosphodiesterase-5 (PDE-5) inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline).

WARNINGS AND PRECAUTIONS

Embryo-Fetal Toxicity. Adempas may cause fetal harm when administered during pregnancy and is contraindicated for use in women who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, advise use of acceptable contraception and obtain monthly pregnancy tests. For females, Adempas is only available through a restricted program under the Adempas REMS Program.

Please see additional Important Safety Information, including Boxed Warning, throughout and Brief Summary of Prescribing Information at end of advertisement.

Patients walked farther with Adempas at Week 16: results from Week 2 onward

46m improvement (mean) in 6MWD over placebo at Week 16 (95 % CI: 25m-67m; p<0.0001) for CTEPH* (WHO Group 4) patients.

WHO FUNCTIONAL CLASS

2x

as many CTEPH patients improved WHO Functional Class vs placebo (p=0.0026; Adempas: n=57/173 [33%], placebo: n=13/87 [15%]) at Week 16.

Deteriorated

5 % for Adempas (n=9/173)

7 % for placebo (n=6/87)

Stable

62 % for Adempas (n=107/173)

78 % for placebo (n=68/87)

CHEST-1: 261 CTEPH patients were studied. (Adempas n=173, placebo n=88)
Baseline characteristics:
*Inoperable or recurrent/persistent CTEPH after surgery.

– Mean age: 59 years (range: 18–80)

– Mean 6MWD was 347m

– Concomitant medications: Stable dosages of oral anticoagulants, diuretics, digitalis, calcium channel blockers, and oxygen were allowed, but not nitric oxide donors, endothelin receptor antagonists, prostacyclin analogues, specific phosphodiesterase (PDE)-5 inhibitors (such as sildenafil, tadalafil, or vardenafil), and nonspecific PDE inhibitors (for example, dipyridamole or theophylline)

Patient population was: 72 % inoperable by pulmonary endarterectomy (PEA) (pulmonary vascular resistance [PVR] >300 dyn·sec·cm^{-5} and mean pulmonary arterial pressure >25 mm Hg measured at least 90 days after the start of full anticoagulation); 28 % recurrent or persisting pulmonary hypertension (PH) following PEA (PVR >300 dyn·sec·cm^{-5} measured at least 180 days following PEA). The majority of patients were WHO Functional Class II (31 %) or III (64 %) at baseline. Patients with systolic blood pressure <95 mm Hg were excluded.

WARNINGS AND PRECAUTIONS

Adempas REMS Program. Females can only receive Adempas through the Adempas REMS Program, a restricted distribution program.

Important requirements of the Adempas 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 Adempas REMS Program prior to initiating Adempas. Male patients are not enrolled in the Adempas REMS Program.
- Female patients 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 Adempas.

Further information, including a list of certified pharmacies, is available at www.AdempasREMS.com or 1-855-4ADEMPAS.

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More than 90% of Adempas patients survived at 2 years*

*Data from CHEST-2 and PATENT-2 open-label extension studies. Without a control group, these data must be interpreted cautiously.

PAH

93%

PROBABILITY OF SURVIVAL AT 2 YEARS

CTEPH

94%

PROBABILITY OF SURVIVAL AT 2 YEARS

At 1 year, probability of survival was 97% in both open-label extension studies.

WARNINGS AND PRECAUTIONS

Hypotension. Adempas reduces blood pressure. Consider the potential for symptomatic hypotension or ischemia in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, or concomitant treatment with antihypertensives or strong CYP and P-gp/BCRP inhibitors. Consider a dose reduction if patient develops signs or symptoms of hypotension.

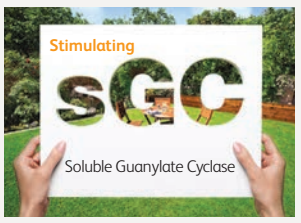
Bleeding. In the placebo-controlled clinical trials, serious bleeding occurred in 2.4% of patients taking Adempas compared to 0% of placebo patients. Serious hemoptysis occurred in 5 (1%) patients taking Adempas compared to 0 placebo patients, including one event with fatal outcome. Serious hemorrhagic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

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.

MOST COMMON ADVERSE REACTIONS

- The most common adverse reactions occurring more frequently (≥3%) on Adempas than placebo were headache (27% vs 18%), dyspepsia/gastritis (21% vs. 8%), dizziness (20% vs 13%), nausea (14% vs 11%), diarrhea (12% vs 8%), hypotension (10% vs 4%), vomiting (10% vs 7%), anemia (7% vs 2%), gastroesophageal reflux disease (5% vs 2%), and constipation (5% vs 1%).
- Other events that were seen more frequently in Adempas compared to placebo and potentially related to treatment were: palpitations, nasal congestion, epistaxis, dysphagia, abdominal distension and peripheral edema.

For important risk and use information, please see the Brief Summary of the full Prescribing Information, including Boxed Warning, on the next page.



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400-10-0003-14b September 2014

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

BRIEF SUMMARY of PRESCRIBING INFORMATION

For additional information, please see the full Prescribing Information at www.adempas-us.com.

WARNING: EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning

- **Do not administer Adempas to a pregnant female because it may cause fetal harm. (4.1, 5.1, 8.1)**
- **Females of reproductive potential: Exclude pregnancy before start of treatment, monthly during treatment, and 1 month after treatment discontinuation. Prevent pregnancy during treatment and for one month after treatment discontinuation by use of acceptable methods of contraception. (2.3, 5.1, 5.2, 8.6)**
- **For females, Adempas is available only through a restricted program called the Adempas REMS Program. (5.1, 5.2).**

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 (61%) 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 while taking this drug, the patient should be apprised of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*.

4.2 Nitrates and Nitric Oxide Donors

Co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated *[see Drug Interactions (7.1) and Clinical Pharmacology (12.2)]*.

4.3 Phosphodiesterase Inhibitors

Concomitant administration of Adempas with specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline) is contraindicated *[see Drug Interactions (7.1) and Clinical Pharmacology (12.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

Adempas may cause fetal harm when administered during pregnancy and is contraindicated for use in women who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, advise use of acceptable contraception and obtain monthly pregnancy tests. For females, Adempas is only available through a restricted program under the Adempas REMS Program *[see Dosage and Administration (2.3), Warnings and Precautions (5.2) and Use in Specific Populations (8.1, 8.6)]*.

5.2 Adempas REMS Program

Females can only receive Adempas through the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program, a restricted distribution program *[see Warnings and Precautions (5.1)]*.

Important requirements of the Adempas 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 Adempas REMS Program prior to initiating Adempas. Male patients are not enrolled in the Adempas REMS Program.
- Female patients of reproductive potential must comply with the pregnancy testing and contraception requirements *[see Use in Specific Populations (8.6)]*.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive Adempas.

Further information, including a list of certified pharmacies, is available at www.AdempasREMS.com or 1-855-4 ADEMPAS.

5.3 Hypotension

Adempas reduces blood pressure. Consider the potential for symptomatic hypotension or ischemia in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, or concomitant treatment with antihypertensives or strong CYP and P-gp/BCRP inhibitors *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*. Consider a dose reduction if patient develops signs or symptoms of hypotension.

5.4 Bleeding

In the placebo-controlled clinical trials, 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 catheter site hemorrhage, and 1 each with subdural hematoma, hematemesis, and intra-abdominal hemorrhage.

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.

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 reactions 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 (Pooled from CHEST-1 and PATENT-1)

Adverse Reactions	Adempas % (n=490)	Placebo % (n=214)
Headache	27	18
Dyspepsia and Gastritis	21	8
Dizziness	20	13
Nausea	14	11
Diarrhea	12	8
Hypotension	10	4
Vomiting	10	7
Anemia (including laboratory parameters)	7	2
Gastroesophageal reflux disease	5	2
Constipation	5	1

Other events that were seen more frequently in Adempas compared to placebo and potentially related to treatment were: palpitations, nasal congestion, epistaxis, dysphagia, 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

7.1 Pharmacodynamic Interactions with Adempas

Nitrates: Co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated because of hypotension *[see Contraindications (4.2) and Clinical Pharmacology (12.2)]*.

PDE Inhibitors: Co-administration of Adempas with specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) and nonspecific PDE inhibitors (such as dipyridamole or theophylline), is contraindicated because of hypotension *[see Contraindications (4.3) and Clinical Pharmacology (12.2)]*. Clinical experience with co-administration of Adempas and

other phosphodiesterase inhibitors (for example, milrinone, cilostazole, roflumilast) is limited.

7.2 Pharmacokinetic Interactions with Adempas

Smoking: Plasma concentrations in smokers are reduced by 50-60% compared to nonsmokers. Based on pharmacokinetic modeling, for patients who are smokers, doses higher than 2.5 mg three times a day may be considered in order to match exposure seen in nonsmoking patients. Safety and effectiveness of Adempas doses higher than 2.5 mg three times a day have not been established. A dose reduction should be considered in patients who stop smoking *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

Strong CYP and P-gp/BCRP inhibitors: Concomitant use of riociguat with strong cytochrome CYP inhibitors and P-gp/BCRP inhibitors such as azole antimycotics (for example, ketoconazole, itraconazole) or HIV protease inhibitors (such as ritonavir) increase riociguat exposure and may result in hypotension. Consider a starting dose of 0.5 mg 3 times a day when initiating Adempas in patients receiving strong CYP and P-gp/BCRP inhibitors. Monitor for signs and symptoms of hypotension on initiation and on treatment with strong CYP and P-gp/BCRP inhibitors. A dose reduction should be considered in patients who may not tolerate the hypotensive effect of riociguat *[see Dosage and Administration (2.5), Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

Strong CYP3A inducers: Strong inducers of CYP3A (for example, rifampin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) may significantly reduce riociguat exposure. Data are not available to guide dosing of riociguat when strong CYP3A inducers are co-administered *[see Clinical Pharmacology (12.3)]*.

Antacids: Antacids such as aluminum hydroxide/magnesium hydroxide decrease riociguat absorption and should not be taken within 1 hour of taking Adempas *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

Risk Summary

Adempas may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. Adempas was teratogenic and embryotoxic in rats at doses with exposures to unbound drug that were approximately 8 times and 2 times, respectively, the human exposure. In rabbits, riociguat led to abortions at 4 times the human exposure and fetal toxicity with exposures approximately 13 times the human exposure. If Adempas is used in pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus *[see Boxed Warning and Contraindications (4.1)]*.

Animal Data

In rats administered riociguat orally (1, 5, and 25 mg/kg/day) throughout organogenesis, an increased rate of cardiac ventricular-septal defect was observed at the highest dose tested. The highest dose produced evidence of maternal toxicity (reduced body weight). Post-implantation loss was statistically significantly increased from the mid-dose of 5 mg/kg/day. Plasma exposure at the lowest dose in which no adverse effects were observed is approximately 0.4 times that in humans at the maximally recommended human dose (MRHD) of 2.5 mg three times a day based on area under the time-concentration curve (AUC) for unbound drug in rat and humans. Plasma exposure at the highest dose (25 mg/kg/day) is approximately 8 times that in humans at the MRHD while exposure at the mid-dose (5 mg/kg/day) is approximately 2 times that in humans at the MRHD. In rabbits given doses of 0.5, 1.5 and 5 mg/kg/day, an increase in spontaneous abortions was observed starting at the middle dose of 1.5 mg/kg, and an increase in resorptions was observed at 5 mg/kg/day. Plasma exposures at these doses were 4 times and 13 times, respectively, the human exposure at the MRHD.

8.3 Nursing Mothers

It is not known if Adempas is present in human milk. Riociguat or its metabolites were present in the milk of rats. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from riociguat, discontinue nursing or Adempas.

8.4 Pediatric Use

Safety and effectiveness of Adempas in pediatric patients have not been established *[see Nonclinical Toxicology (13.2)]*.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of Adempas, 23% were 65 and over, and 6% were 75 and over *[see Clinical Studies (14)]*. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Elderly patients showed a higher exposure to Adempas *[see Clinical Pharmacology (12.3)]*.

8.6 Females and Males of Reproductive Potential

Pregnancy Testing: Female patients of reproductive potential must have a negative pregnancy test prior to starting treatment with Adempas, monthly during treatment, and one month after discontinuation of treatment with Adempas. Advise patients to contact their healthcare provider if they become pregnant or suspect they may be pregnant. Counsel patients on the risk to the fetus *[see Boxed Warning, Dosage and Administration (2.3) and Use in Specific Populations (8.1]*.

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

8.7 Renal Impairment

Safety and efficacy have not been demonstrated in patients with creatinine clearance <15 mL/min or on dialysis *[see Clinical Pharmacology (12.3)]*.

8.8 Hepatic Impairment

Safety and efficacy have not been demonstrated in patients with severe hepatic impairment (Child Pugh C) *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

In cases of overdose, blood pressure should be closely monitored and supported as appropriate. Based on extensive plasma protein binding, riociguat is not expected to be dialyzable.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Embryo-Fetal Toxicity

Instruct patients on the risk of fetal harm when Adempas is used during pregnancy *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]*. Instruct females of reproductive potential to use effective contraception and to contact her physician immediately if they suspect they may be pregnant. Female patients must enroll in the Adempas REMS Program.

Adempas REMS Program

For female patients, Adempas is available only through a restricted program called the Adempas REMS Program *[see Warnings and Precautions (5.2)]*. Male patients are not enrolled in the Adempas REMS Program.

Inform female patients (and their guardians, if applicable) of the following important requirements:

- All female patients must sign an enrollment form.
- Advise female patients of reproductive potential that she must comply with the pregnancy testing and contraception requirements *[see Use in Specific Populations (8.6)]*.
- Educate and counsel females of reproductive potential on the use of emergency contraception in the event of unprotected sex or contraceptive failure.
- Advise pre-pubertal females to report any changes in their reproductive status immediately to her prescriber.

Review the Medication Guide and REMS educational materials with female patients.

Other Risks Associated with Adempas

- Inform patients of the contraindication of Adempas with nitrates or nitric oxide donors or PDE-5 inhibitors.
- Advise patients about the potential risks/signs of hemoptysis and to report any potential signs of hemoptysis to their physicians.
- Instruct patients on the dosing, titration, and maintenance of Adempas.
- Advise patients regarding activities that may impact the pharmacology of Adempas (strong multi pathway CYP inhibitors and P-gp/BCRP inhibitors and smoking). Patients should report all current medications and new medications to their physician.
- Advise patients that antacids should not be taken within 1 hour of taking Adempas.
- Inform patients that Adempas can cause dizziness, which can affect the ability to drive and use machines *[see Adverse Reactions (6.1)]*. They should be aware of how they react to Adempas, before driving or operating machinery and if needed, consult their physician.

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PRESIDENT'S REPORT Reflecting on a year of focus and teamwork

BY DR. MICHAEL H. BAUMANN, FCCP

The presidential cycle is coming full circle. My year will nearly be done when you read this. And it has been a great year! I truly appreciate this opportunity – thank you.

Congratulations to Curt Sessler on his impending year as President of CHEST, and thank you to Darcy Marciniuk for his 4 very productive years in the presidential line up. And, welcome to Dr. Gerard Silvestri, FCCP, as our new President-Designate. And Barb Phillips, you have only one more year until you fill what will no doubt be a big pair of shoes left by Curt!

DR. BAUMANN

Last October, my incoming President's speech and my May article in *CHEST Physician* highlighted focus and teamwork. We have a great staff team at CHEST led by our talented CEO, Paul Markowski, and a very capable and dedicated Board of Regents. We have much to be proud of this year that could not have been accomplished without this team and all of you, our members. We have strengthened the past hard work of this collaborative team and continued our focus on our guiding strategic plan. Our crowning accomplishment this year (among many) was the official opening of our new global headquarters in February, on time and on budget! We celebrated our grand opening and ribbon cutting in April. Our leadership in simulation training, acknowledged by our accreditation by the Society of Simulation in Healthcare (SSH) in August 2013, is enhanced by our new Innovation, Simulation, and Training Center as part of our new headquarters. We are on track to offer even more innovative programs in simulation education through our center in 2015. Check out the many great offerings on our website at chestnet.org.

Our new branding program [see logo, shown at right], launched during CHEST 2013, was seamlessly and successfully implemented this year with excellent feedback. Our journal, our website,

CHEST

We celebrated the official opening of our new global headquarters in February, on time and on budget! It was smiles all around at the ribbon-cutting ceremony in April in Glenview, Illinois.

and many other areas have a fresh new look that complements our many other forward-facing programs. Our CHEST Enterprises team has continued to grow during its first full year of operation, successfully offering educational opportunities to our partners in industry.

Our "brain," the new association management system (AMS), is slated for launch in May 2015. The AMS will connect members to a robust knowledge management system heightening CHEST educational experiences, our premier offering as an organization. One such premier global educational offering occurred in Madrid last March with our first CHEST World Congress (CWC) in many years. Thank you to the skillful leadership of our organizing committee and our co-chairs, Dr. Joan Soriano and Dr. Richard Irwin. The success of the Madrid CWC is significant, and we are working on an even better (if that's possible!) CWC to be held in China in 2016. Stay-tuned for more details. This China CWC nicely complements our ongoing pulmonary and critical care medicine fellowship training program in China, successfully launched last July.

CHEST 2014 in Austin this month promises gainful education and great connections. Thanks to the hard work of our scientific program chair, Dr.Mark Metersky, and our program committee, the excellent program includes simulation offerings, problem-based learning opportunities, poster discussion sessions, and much more. Please join us in Austin to enjoy world-class education, barbeque, and music (maybe not in that exact order)!

Our journal *CHEST*, under the able leadership of our editor in chief, Dr. Richard Irwin, reached new heights with an impact factor of 7.132 (from 5.85), the highest in the history of the journal. This now places *CHEST* in second place among 27 critical care journals and third place among 53 respiratory journals. Congratulations to our journal team and to you, our contributing authors.

Our CHEST Foundation, under the leadership of John Studdard, has seen significant strides this year, including a re-energized giving program on the heels of a very successful capital campaign for our new global headquarters. Make a donation today, and see your dollars working toward improving respiratory health!

All of these successes, with more to come, have occurred with a disciplined focus, by our CHEST team, on our collaboratively developed strategic plan and with a continued focus on financial awareness. Throughout this successful year, some of our staff team members have had the opportunity to move on to new challenges and opportunities—we wish them the best while we get to know the new talented members of our team. Please join me in welcoming these new team members and wishing our old friends the best in their new endeavors!

So did focus and teamwork pay off? A resounding. . .Yes! And, with the continued support of our members, boards, and staff, our great team will continue to offer the best in pulmonary, critical care, and sleep medicine education. Thank you again for the opportunity to serve as your CHEST President. It has been a great year!

PULMONARY PERSPECTIVES Non-CF bronchiectasis: Emerging trends

BY DR. DIEGO J. MASELLI, FCCP

Over the past few decades, there has been a considerable increase in interest and awareness of non-cystic fibrosis bronchiectasis (NCFB). Previously considered an "orphan" lung diagnosis, it seems that this condition is more common than we thought. This is partly due to the improvement in quality and increased availability of thoracic imaging. For example, a CT of the chest provides far more detail regarding the location, distribution, and morphological features of the bronchiectatic airways and may identify subtle abnormalities that a chest radiograph may not. Another reason is that often CTs, performed for reasons other than respiratory complaints, find "incidental" bronchiectasis, thereby increasing the incidence of NCFB. These patients may have extensive disease presentations with surprising minimal symptoms (Kwak et al. *Tohoku J Exp Med*. 2010;222[4]:237). Finally, and perhaps more troublesome, it is possible that the change in the incidence of NCFB may be due to an increase in microbiological resistance or virulence, alteration in the epidemiological patterns of autoimmune diseases, or other undetermined environmental factors.

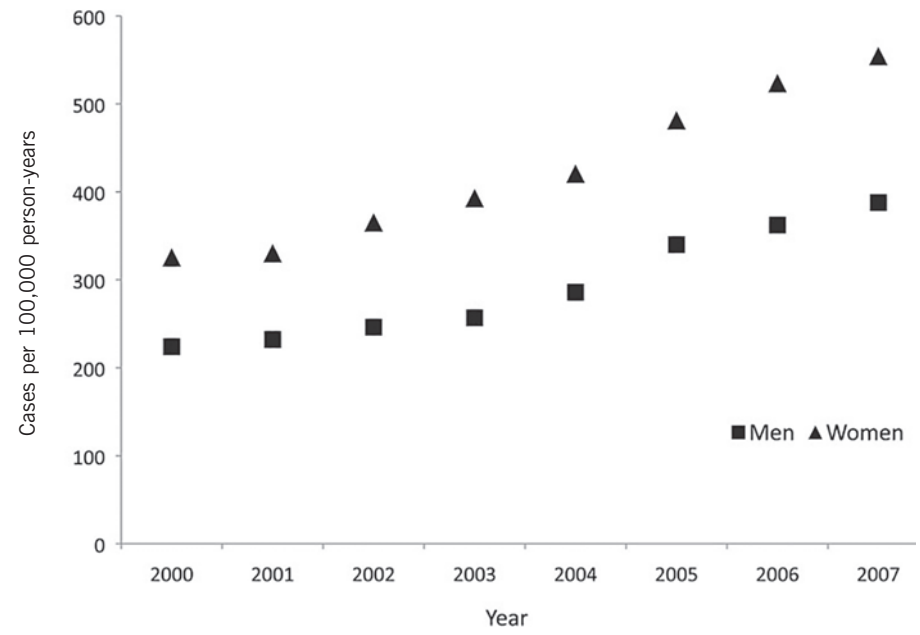
DR. MASELLI

Regardless of the reason, it is clear that incidence of NCFB is increasing, and these patients often require more medical care and have worse outcomes (Seitz et al. *Chest*. 2012;142[2]:432). NCFB can be caused by a plethora of conditions: ranging from the infections (eg, TB) to the autoimmune diseases (eg, rheumatoid arthritis [RA]) to deficiencies in the immune system (eg, common variable immunodeficiency). Nevertheless, in some cases an etiology or association cannot be determined. The pathogenesis of bronchiectasis is well-established: an initial insult leads to an inflammatory response, resulting in permanent dilation of the airways. This in turn causes accumulation of secretions and eventually colonization/infection, leading to more inflammation and dilation of the airways. This is known as the bronchiectasis "vicious cycle."

In an infection (for example, TB), the initial insult is readily identifiable: activated macrophages and lymphocytes release cytokines in combination with bacterial products that, when severe enough, lead to permanent changes in the architecture of the lung. However, it remains misunderstood why not all TB infections lead to bronchiectasis. Is there a genetic predisposition? In other conditions, the initial insult is less clear. For example, why is RA a risk for bronchiectasis? Is there a truly direct causal relationship? Some authors have suggested that perhaps the medications used for the treatment of RA increased the likelihood of an infection. Others have suggested a direct antigen-antibody interaction. But to this date, no clear cause has been identified. This is unfortunately the case with the majority of causes of bronchiectasis; the initial insult remains a mystery.

Diagnosis

Guidelines for the diagnosis and management of NCFB have been published and provide a framework for the approach to these patients (Pasteur et al. *Thorax*. 2010;65[7]:577). Nevertheless, there are still several areas that require further study and many of the guideline recommendations are derived from expert opinions or small studies. Light has recently been shed on some areas of uncertainty, but other questions remain unanswered.



Trend in annual prevalence of bronchiectasis by gender in the United States.

Do we need to rule out every single diagnostic possibility when we encounter a patient with NCFB? Moreover, does it really make a difference if we actually identify an etiology? Because there is a long list of etiologies that can cause bronchiectasis, testing may have a substantial economic burden and may not necessarily change the management or outcomes in NCFB. Some experts advocate a case-by-case approach and recommend relying heavily on the history and physical exam, while others believe this strategy fails to identify a large portion of etiologies. Other leading experts in this field advocate extensive testing. The percentage of idiopathic bronchiectasis varies widely, mostly because of the variability of testing used in older studies, and different patient populations, and those that vary by geographic location. These studies have not found an association between the etiology and mortality, but a recent study revealed that idiopathic bronchiectasis may have decreased mortality (Goeminne et al. *Respir Res*. 2012;16[13]:21). In contrast, patients with a coexisting diagnosis of COPD have the highest mortality (Goeminne et al. *Respir Med*. 2014;108[2]:287).

Ongoing studies are determining the impact of comprehensive vs directed protocols for the diagnosis of the etiology of NCFB.

Treatment

Can we use therapies effective in other diseases in our NCFB patients? Because of the relative paucity of studies with large case series, some of the treatment modalities for NCFB patients have been extrapolated from COPD, cystic fibrosis (CF), and other chronic pulmonary conditions. For example, airway clearance techniques that have been effective in CF, such as the vibratory vest, have also been effective in patients with NCFB. But caution should be exercised, because not all successful therapies for other disorders can be applied to NCFB. Recombinant human DNase, for instance, has been shown to improve lung function in CF, but was ineffective and potentially harmful in NCFB (O'Donnell et al. *Chest*. 1998;113[5]:1329).

What have we learned about the therapies specifically studied in NCFB patients? As the incidence of bronchiectasis has risen, studies with larger case series have provided new evidence. Macrolides, which have both antimicrobial and anti-inflammatory properties, have been found to have a significant impact on NCFB. A meta-analysis of nine trials showed that macrolides improved exacerbation rates, respiratory symptoms, and pulmonary function compared with placebo (Wu et al. *Respirology*. 2014;19[3]:321). This ther-

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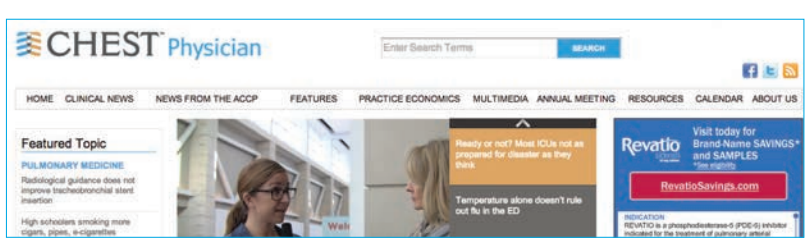

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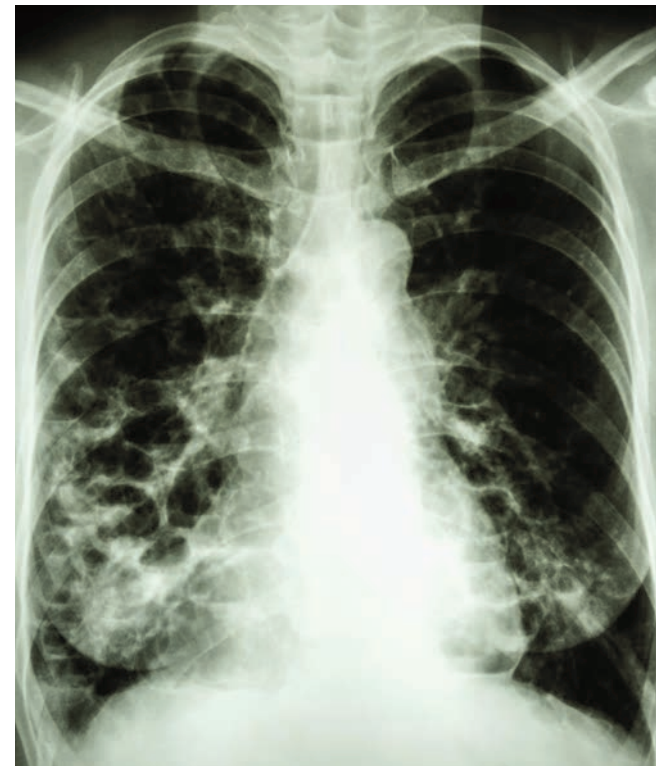
apy probably has a greater impact on the "frequent exacerbators," and microbiological patterns of resistance continue to be a concern, but results from these studies continue to show promise.

Are inhaled antibiotics effective in NCFB? This therapy has the advantage of enhanced drug delivery at the target site, less systemic toxic effects, and relatively easier delivery. Several antibiotics have been evaluated recently with promising results. Treatment with dual release liposomal ciprofloxacin reduced bacterial density of *Pseudomonas aeruginosa* and delayed the time to the first exacerbation (Serisier et al. *Thorax*. 2013;68[9]:812). In another study, 6 months of inhaled colistin also showed a reduction in the density of *P aeruginosa* and improvement in respiratory symptoms, but did not affect the time to exacerbation significantly (Haworth et al. *Am J Respir Crit Care Med*. 2014;189[8]:975). Similar results have been observed in smaller trials with nebulized tobramycin and gentamicin. All of these inhaled antibiotics have an adequate safety profile and are tolerated well for the most part. The trials to date are of modest size, and larger confirmatory trials are still needed to provide firm recommendations. Nevertheless, it appears that maintenance therapy with nebulized antibiotics, especially in the setting of *P aeruginosa* infection or colonization, will continue to gain acceptance.

What other therapies are there beyond antibiotics and airway clearance techniques? For those patients with recurrent exacerbations or pathogens that are difficult to eradicate (eg, atypical mycobacteria), surgical resection of localized bronchiectatic airways can be considered. With the aid of video-assisted thoracoscopic resection, specialized centers have been very successful in minimizing complications in patients with localized bronchiectasis (Mitchell et al. *Ann Thorac Surg*. 2012;93[4]:1033). Unfortunately, diffuse bronchiectasis is more commonly present, limiting the utility of surgical resection. Finally, statins have been associated with improved symptoms in patients with stable bronchiectasis, but future studies are needed to confirm these findings (Mandal et al. *Lancet Respir Med*. 2014;2[6]:455).



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Can we use therapies effective in other diseases in our non–cystic fibrosis bronchiectasis patients?

Conclusions

The trends in how we utilize imaging of the chest have caused a paradigm shift in our recognition and approach to NCFB. While purists will argue that bronchiectasis is a clinical/radiological diagnosis, more often than not, we are encountering patients with advanced NCFB with minimal or no symptoms. How to best approach these patients with few or no symptoms is an area of ongoing debate. Further studies are required to identify risk factors for poor outcomes and complications in this population. We eagerly await the evaluation of algorithms of ongoing registries so that we can implement a cost-effective, evidence-based workup for our patients. Newer therapies, such as macrolides and other inhaled antibiotics (as well as statins, potentially), offer new treatment strategies in the perplexing world of NCFB.

Dr. Maselli is Assistant Professor of Medicine, Division of Pulmonary Diseases & Critical Care, University of Texas Health Science Center at San Antonio, San Antonio, Texas.

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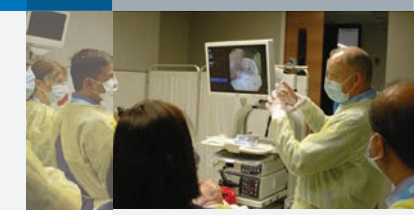

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NETWORKS EBUS-TNA guidance, enterovirus watch, CPET

Interventional Chest/ Diagnostic Procedures

EBUS-TNA consensus ahead

There have been more than 1,000 manuscripts published on endobronchial ultrasound; although many questions have been answered, there still is great debate as to what is the "best" way to perform the procedure, especially from an evidence-based medicine standpoint. The Interventional Chest/Diagnostic Procedure NetWork has been given the "green light" by the CHEST Guidelines Oversight Committee (GOC) to begin work on a consensus statement regarding best practices for endobronchial ultrasound-guided transbronchial needle aspiration.


DR. FELLER-KOPMAN

Lead by Dr. Momen Wahidi (Immediate Past Chair of the NetWork) with a group of 10 international thought leaders, the committee began combing through the world's literature to examine the data regarding 13 key questions, such as deep vs moderate sedation, number of needle passes required, the use of suction vs no suction, and the use of rapid on-site cytologic evaluation (ROSE). The process has been greatly facilitated by CHEST staff and includes the support of search strategists and professional methodologists. As per prior CHEST guidelines, this will utilize the PICO format for review: identify the patient population studied, the intervention, control, and outcome assessed. Each manuscript will be also be reviewed for potential conflicts of interest, and specific limitations of each study will be identified.

As with the *Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines*, it is our goal to provide our membership with the highest quality evidence to improve the care of our patients. We hope to have a completed document in 2015.

Dr. David Feller-Kopman, FCCP, Chair
Dr. Momen Wahidi, FCCP, Ex Officio

Pediatric Chest Medicine

Facing a pandemic

As Africa is struggling to contain an unprecedented Ebola outbreak, children in the United States are also facing a pandemic. Enterovirus D68 (EV-D68) was first identified in California in 1962 but has not been commonly identified as a pathogen in the United States until the last few weeks. The virus may cause fever and malaise, along with mild-to-severe respiratory symptoms, including rhinorrhea, cough, and bronchospasm (Midgley et al. *MMWR*. 2014:63[36]:798).

While respiratory viruses are often most aggressive in the very young and very old, early reports suggest EV-D68 primarily affects infants, children, and dolescents. At particular risk appear to be children with a history of lower airways disease, including children with asthma and former premature infants. As I write this, our Children's Hospital is filling up with patients suffering from viral respiratory symptoms, including bronchiolitis and asthma

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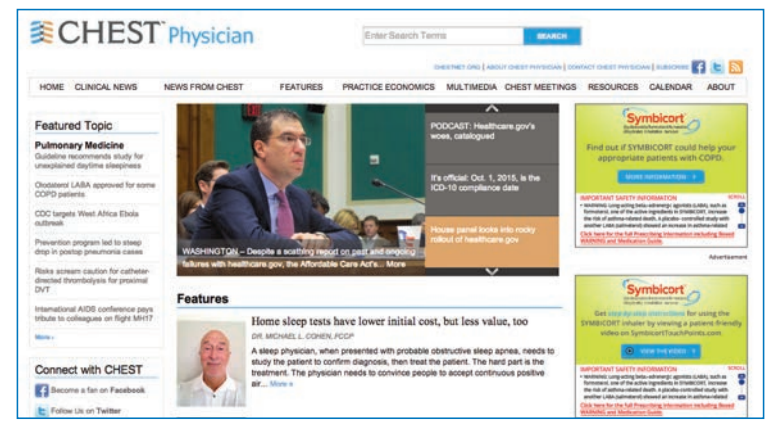

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exacerbations. In lieu of rapid detection assays, we are waiting on viral cultures to confirm the diagnosis.

We will know more about EV-D68 in the weeks and months to come; our knowledge will have significantly grown by the time this article is published. Prevention of spreading the virus and public health education will be necessary for containment. While it may lead to critical illness, EV-D68 fortunately does not appear to be as virulent as the 2009 H1N1 influenza strain. Noninvasive ventilation, including high-flow nasal cannula, may be helpful to many patients hospitalized with EV-D68. It is clear that resource utilization will be of utmost importance, given the rapid spread of the virus and the propensity to affect children of all ages.

DR. REHDER

Dr. Kyle J. Rehder, FCCP
Steering Committee Member

Pulmonary Physiology, Function, and Rehabilitation

Cardiopulmonary exercise coming to an office near you

In healthy people, predictable physiologic changes occur during exercise. In other words, the ability to perform physical exercise is critically related to the cardiovascular system's capacity to supply oxygen to the muscles and the pulmonary system's ability to clear CO_2 from the blood via the lungs. Consequently, maximal cardiopulmonary exercise testing (CPET) provides valuable diagnostic and prognostic information regarding patients with cardiovascular and pulmonary disease by assessing the integrative exercise responses involving the pulmonary, cardiovascular, and skeletal muscle systems, which are not adequately reflected through the measurement of individual organ system function.

However, patient's performance may be limited because of pain or fatigue, severe dyspnea on exertion, and osteoarthritic limitations; maximal exercise testing may even be contraindicated at times. As such, submaximal CPET is being increasingly proposed as an alternative. The test takes 6 minutes, fits well in an office setting, and involves measuring parameters, such as ventilatory efficiency V_E/Vco_2, oxygen pulse (Vo_2/HR), oxygen uptake efficiency (Vo_2/log V_E), and partial pressure of end-tidal carbon dioxide ($ETco_2$), which have already been shown to carry significant prognostic value. Examples in the application of the submaximal cardiopulmonary exercise are follow-up to pulmonary arterial hypertension, congestive heart failure, and the assessment of patient response to pharmaceutical or medical device therapy (or the effect of pulmonary or cardiac rehabilitation). As the technology matures and more data are obtained in each disease process, the office-based submaximal CPET will surely find its place in the algorithm of dyspnea diagnosis or treatment monitoring.

DR. BENCHEQROUN

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Dr. Hassan Bencheqroun, FCCP
Vice-Chair

Pulmonary Vascular Disease

CHEST endorses PHA Pulmonary Hypertension Care Center program

CHEST has endorsed the Pulmonary Hypertension Association's (PHA) Pulmonary Hypertension Care Center (PHCC) accreditation program. As part of this endorsement, CHEST will have a nonvoting member of the PHCC Oversight Committee. The PHCC program is designed to align physicians, patients, and caregivers in the effort to improve diagnosis, evaluation, understanding, and collaboration in the care of patients with pulmonary hypertension (PH). This program has the goal of increasing the awareness and compliance with PH diagnostic and therapeutic guidelines while improving care and collaboration.

With the Pulmonary Arterial Hypertension Quality Enhancement Research Initiative Extension Program (PAH QuERI) study, it became clear that compliance with diagnostic guidelines was often incomplete. This program is designed to identify centers to promote excellence of care. It will require an application, a site visit, and participation in ongoing data collection. It is hoped that it will improve quality of care in patients with PH. In addition, the PHCC program will eventually develop a registry at the care centers to allow additional treatment and demographic, diagnostic, and outcome data.

DR. TEST

CHEST endorsement is an important step because it will give the organization a role in the development, implementation, and evolution of this program. The Pulmonary Vascular Disease NetWork of CHEST feels that this is a positive move that will allow the CHEST organization to participate more thoroughly in the future policies of PH care.

Dr. Victor Test, FCCP, Chair

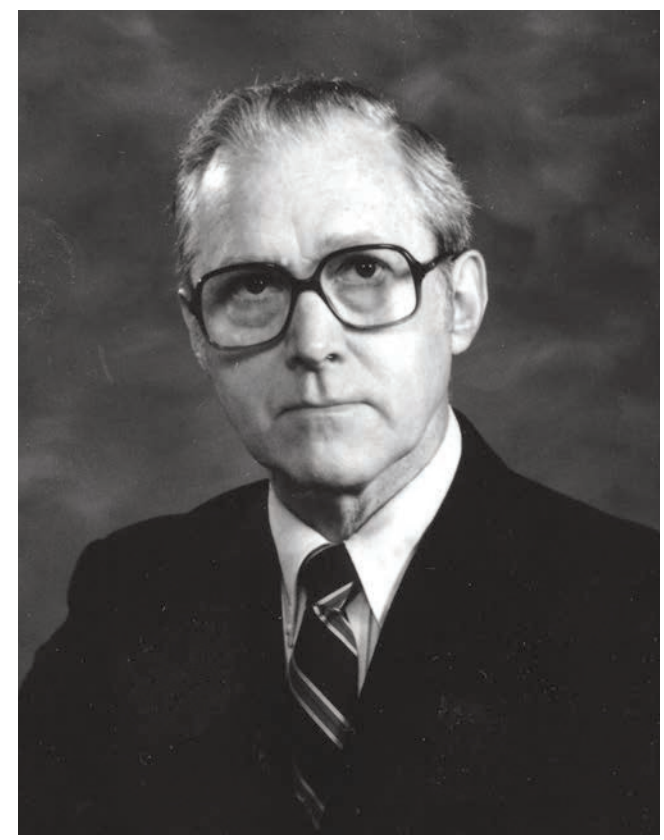
NetWorks *continued on page 34*

In remembrance: Dr. Joseph Comer Ross

Joseph Comer Ross, MD, FCCP, a Past President of the American College of Chest Physicians (CHEST), died in Nashville on June 22, 2013. An Army veteran of WW II, Dr. Ross graduated from the University of Kentucky and earned his MD at Vanderbilt Medical School. After completing a residency at Duke Medical School, he began a distinguished career in academic medicine at Indiana University (1958-1970) where, continuing the research he began at Duke, he helped establish the connection between smoking and lung cancer. From 1970-1980, he served the Medical University of South Carolina as Medical Director and Chair of the Department of Medicine. While at MUSC, Dr. Ross earned national recognition for his expertise in pulmonary medicine and was elected President of the American College of Chest Physicians in 1977. Dr. Ross finished his professional career as Associate Vice Chancellor for Medical Affairs at his alma mater, Vanderbilt University Medical Center (1982-1999).

In addition to his presidential role, Dr. Ross served CHEST throughout his career in such positions as Chair of the Council of Governors, Chair of the Bylaws Committee, and member of the Nominating Committee and Credentials Committee.

CHEST extends its heartfelt condolences to the Ross family.



CHEST

Dr. Ross served as President of the American College of Chest Physicians 1977-1978.

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

Help Your Patients Breathe Better With ANORO ELLIPTA

Indication

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

Important Safety Information for ANORO ELLIPTA

WARNING: ASTHMA-RELATED DEATH

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

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

Once-daily ANORO ELLIPTA

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

Important Safety Information for ANORO ELLIPTA (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

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

ADVERSE REACTIONS

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

DRUG INTERACTIONS

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

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

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

ANORO ELLIPTA was developed in collaboration with Theravance

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

BRIEF SUMMARY

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

WARNING: ASTHMA-RELATED DEATH

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

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

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

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

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

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

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

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

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

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

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

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

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

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

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

7.3 Beta-Adrenergic Receptor Blocking Agents

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

7.4 Non–Potassium-Sparing Diuretics

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

7.5 Anticholinergics

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

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

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

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

8.2 Labor and Delivery

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

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

8.3 Nursing Mothers

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

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

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

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

8.6 Hepatic Impairment

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

8.7 Renal Impairment

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

10 OVERDOSAGE

No case of overdose has been reported with ANORO ELLIPTA.

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

10.1 Umeclidinium

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

10.2 Vilanterol

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

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

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

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

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

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

17 PATIENT COUNSELING INFORMATION

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

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

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

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

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

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

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

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

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

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

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

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

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ANORO ELLIPTA was developed in collaboration with Theravance.

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Research Triangle Park, NC 27709

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NetWorks *continued from page 29*

Thoracic Oncology

Lung cancer screening advocacy

It is an exciting time to be interested in thoracic oncology, and we would like to inform you about some of the activities of the Thoracic Oncology NetWork.

We have recently collaborated with the Thoracic Oncology Assembly of the American Thoracic Society (ATS) to develop a policy statement describing the components that each lung cancer-screening program should have in place in order to provide high-quality screening. Separately, we contributed to a more pragmatic guide to developing a lung cancer-screening program, produced as part of an ATS workshop led by Renda Weiner.

The goals of the policy statement and program guide are to help inform clinicians and CMS in their upcoming decision about coverage of the screening test for the Medicare population.

The goals of these documents are to help inform CMS in their upcoming decision about coverage of the screening test for the Medicare population and to provide clinicians who intend to develop screening programs with guidance and support.

In addition, we have recently published the results of a NetWork project that developed quality indicators for the diagnosis and staging of lung cancer.

Please visit our e-Community site where Lynn Tanoue (our incoming NetWork Chair) has developed a process that will help connect our members to the authors of the Lung Cancer III Guidelines. We look forward to many great sessions at CHEST 2014, including a presentation from Nichole Tanner at our NetWork open meeting.

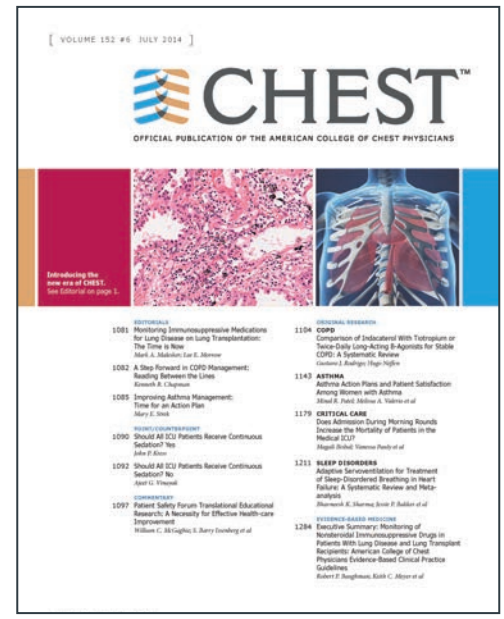
Finally, we would like to congratulate Anil Vachani for his selection as our incoming Vice-Chair, as well as to our five new steering committee members. We encourage anyone with an interest in thoracic oncology to reach out to us and get involved in our activities.

Dr. Peter Mazzone, FCCP, Chair

This month in *CHEST*: Editor's picks

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

EVIDENCE-BASED MEDICINE: COMMENTARY
Overview of the Management of Cough: CHEST Guideline and Expert Panel Report.
By Dr. R. S. Irwin et al.



COMMENTARY
Ventilator-Associated Pneumonia Prevention Methods Using Topical Antibiotics : Herd,Protection or Herd Peril? *By Dr. J. C. Hurley*

ORIGINAL RESEARCH
Chinese Water-Pipe Smoking and the Risk of COPD. *By Dr. J. She et al.*

Dobutamine Stress Echocardiography for the Assessment of Pressure-Flow Relationships of the Pulmonary Circulation.
By Dr. E. M. T. Lau et al.

A Randomized Controlled Trial of Angiotensin-Converting Enzyme Inhibition for Skeletal Muscle Dysfunction in COPD.
By Dr. D. Shrikrishna et al.

EDITORIAL
Care of the Critically Ill and Injured During Pandemics and Disasters: Groundbreaking Results from the Task Force on Mass Critical Care.
By Dr. C. E. Sandrock.

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CHEST FOUNDATION

Donated CPAP machines available to needy

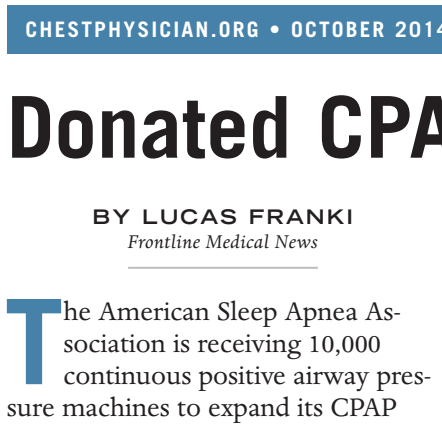
BY LUCAS FRANKI
Frontline Medical News

The American Sleep Apnea Association is receiving 10,000 continuous positive airway pressure machines to expand its CPAP Assistance Program, according to Tracy Nasca, executive director of the ASAA.

The machines are being donated by ResMed, a manufacturer of sleep disorder management devices. "Making CPAPs [continuous positive airway pressure machines] accessible to those who are in need helps us in our mission," ResMed CEO Mick Farrell said in a written statement.

"A donation of this magnitude is unprecedented," said Ms. Nasca in the statement. "The number of patients that will be touched is truly amazing; their quality of life will be improved, but more importantly, lives will be saved."

The CPAP Assistance Program (CAP) is aimed at sleep apnea patients who are out of work, without insurance, or in other types of financial difficulty who cannot afford the devices they need. Doctors can refer their patients to the CAP website, or they can fill out the applications themselves. There is a $100 fee to cover shipping and handling. If patients are unable to afford the fee, "we don't turn patients away," Ms. Nasca said.



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Those most likely to be afflicted with sleep-disordered breathing are the ones who are the least likely to be able to afford the cost.

A major goal of the ASAA is to expand their A.W.A.K.E (Alert, Well, and Keeping Energetic) network, which helps sleep apnea patients educate and treat themselves, and to incorporate a program aimed at supplying sleep apnea patients in need when disasters strike.

"The ResMed donation will help the ASAA move forward to achieve that goal," Ms Nasca said.

Dr. David Schulman, director of the Emory Healthcare Sleep Laboratory in Atlanta, applauded the donation program: "Obstructive sleep apnea is a disease that predominantly affects the obese. Given the well-documented inverse association between socioeconomic status and body mass index, those most likely to be afflicted with sleep-disordered breathing are those that are least likely to be able to afford the insurance to cover the cost of its therapy. The CPAP assistance program will improve the quality of life and overall health of this population for many years to come."

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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 including 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, Glidescopes, Sonosite Ultrasounds etc)

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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 employee satisfaction rates are among the most admired in the country, and the system is recognized as a national leader in quality healthcare.

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Ideal applicant will have an MD degree; be board-certified in pulmonary medicine, critical care medicine and/or internal medicine; have an excellent record of scholarly activity. As per ACGME criteria, applicant must have maintained an academic faculty appointment for a minimum of five years. Previous program director experience preferred, not required.

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For more information about Bronson or Kalamazoo visit **www.bronsonhealth.com** or **www.kalamazoomi.com**
Interested candidates my contact Cadace Lee at 269-341-8631 or **leeca@bronsonhg.org**

CHA Cambridge Health Alliance

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Pulmonary/Critical Care with Sleep

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Please forward CV's to **Laura Schofield, Senior Director of Physician Recruitment**, Cambridge Health Alliance, 1493 Cambridge Street, Cambridge MA 02139. **Telephone** (617) 665-3553, **Fax** (617) 665-3553 or via **e-mail**: Lschofield@challiance.org. EOE. www.challiance.org

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Contact: Heidi Baka, Physician Recruiter
Baka.heid@marshfieldclinic.org
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3 Physician Pulmonary, Critical care, and Sleep practice is seeking an energetic, motivated BC/BE physician. The practice encompasses outpatient and inpatient care. The group currently has a busy office practice and also manages an accredited sleep lab.
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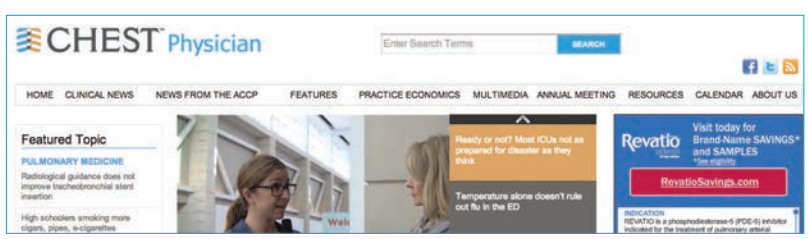

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LDCT screens offer slightly more benefit after age 65

BY MARY ANN MOON
Frontline Medical News

High-risk patients older than 65 years derive slightly more benefit from low-dose CT screening for lung cancer than younger patients do, a study shows

In a secondary analysis of data from the National Lung Screening Trial, low-dose CT (LDCT) screening's positive predictive value, a measure of screening efficiency, was higher in older patients than in those under who were aged 65 years. However, older patients also had slightly greater harms from LDCT screening, mainly because of a slightly higher rate of false-positive results, said Paul F. Pinsky, Ph.D., of the National Cancer Institute and his associates.

The investigators examined this issue because the Centers for Medicare & Medicaid Services has raised the question of whether to cover LDCT costs in this age group, citing concerns that harms may outweigh benefits in the elderly.

The National Lung Screening Trial was the primary source of evidence that the screening reduces lung cancer–specific mortality in patients aged 55-74 years, but only 25% of the participants were over age 65. It has been proposed that older patients, who tend to have more comorbid conditions than younger patients, might incur more complications from diagnostic workups, might be less eligible for curative surgery for screen-detected cancer, and might have elevated postsurgical mortality, which could tip the balance away from benefit and toward harm.

Dr. Pinsky and his associates assessed several facets of LDCT screening according to the age of the participants, comparing the National Lung Screening Trial's findings for 19,612 individuals aged 55-64 years against those for 7,110 patients aged 65-74 years at baseline.

All the participants underwent three annual LDCT screens and were followed for a median of 6.5 years to ascertain lung cancer mortality.

The sensitivity of LDCT in detecting lung cancers was similar between the two age groups, at 93.2% in the under-65 group and 94.3% in the over-65 group. LDCT's positive predictive value was significantly higher in the older group (4.9%) than in the younger group (3.0%), mainly because the older group had a substantially higher prevalence of lung cancer (1.5% vs 0.7%).

Five-year lung cancer–specific survival was only modestly higher for the under-65 group (64%) than for the over-65 group (55%), the investigators reported (Ann. Intern. Med. 2014 Sept. 8 [doi: 10.7326/M14-1484]).

Similar proportions of each group underwent lung resection – 75.6% of the under-65 patients and 73.2% of the over-65 patients. In addition, postsurgical mortality at 90 days was similarly low, at 1.8% in the younger group and 1.0% in the older group. So the concern that many more older than younger patients would be ineligible for curative surgery proved to be unfounded, as did the concern that older patients would experience significantly more harm from resection than younger patients.

On the "harm" side of the balance, the percentage of false-positive results was higher in the older patients (27.7% vs 22.0%), and invasive procedures after false-positive results were slightly more frequent as well (3.3% vs 2.7%). However, the rates of complications resulting from these procedures were similarly low, at 9.8% for the under-65 group and 8.5% for the over-65 group.

"It is difficult to predict how LDCT screening for lung cancer will disseminate in the Medicare-eligible population, regardless of whether it is covered by Medicare. Its use may spread to persons with little chance of benefit and some chance of harm, although this risk exists for those in younger age groups as well.

"Going forward, monitoring and assessing the relative performance of LDCT screening in older persons will be critical to more fully understand its risks and benefits when it is done outside the clinical trial setting, and to modify recommendations on the basis of evidence, if needed," Dr. Pinsky and his associates wrote.

They added that their analysis was limited by the fact that the upper age limit in the National Lung Screening Trial was only 74 years. "This precluded analysis of how persons in their later 70s and 80s fared with LDCT screening," they noted.

VITALS

Key clinical point: Slightly more benefit was found from LDCT lung cancer screening in high-risk patients over age 65 than in younger patients.

Major finding: LDCT's positive predictive value was significantly higher in patients older than 65 years (4.9%) than in those younger than 65 (3.0%), mainly because the older group had a substantially higher prevalence of lung cancer (1.5% vs. 0.7%).

Data source: A secondary analysis of data from the National Lung Screening Trial, involving 19,612 participants aged 55-64 years and 7,110 aged 65-74 years, who had LDCT screening and were followed for about 6 years for the development of lung cancer.

Disclosures: This study was supported by the National Cancer Institute. Dr. Pinsky reported no relevant disclosures. A few coauthors reported financial disclosures involving the National Cancer Institute and various biotechnology companies.

VIEW ON THE NEWS

Dr. W. Michael Alberts, FCCP, comments: One of the concerns identified by the Medicare Evidence Development & Coverage Advisory Committee was the usefulness of low-dose CT screening for lung cancer in the Medicare population.

The National Lung Screening Trial included subjects not yet eligible for Medicare. The study reviewed in this article suggests not only that the test is beneficial in those older than 65 but that slightly more benefit may accrue to high-risk patients of Medicare age compared to the younger cohort. It is my hope that studies such as this will eventually prompt a positive coverage decision.

Patients with extensive SCLC benefit from radiotherapy

BY SUSAN LONDON
Frontline Medical News

SAN FRANCISCO – Patients with extensive small cell lung cancer that responds to chemotherapy fare better when given thoracic radiation in addition to prophylactic cranial irradiation, investigators reported at the annual scientific meeting of the American Society for Radiation Oncology.

"Thoracic radiotherapy – 30 Gy in 10 fractions – improves overall survival, progression-free survival, and intrathoracic control," concluded Dr. Ben J. Slotman, professor and head of the department of radiation oncology at Vrije Universiteit Medical Center, Amsterdam. "We think that this should now be offered in addition to prophylactic cranial irradiation to patients with a response after initial chemotherapy," he said.

"What are your thoughts about building on these results by using perhaps a higher dose of radiation or perhaps radiation to other extrathoracic sites using [stereotactic body radiation therapy] or other approaches like that?" asked session cochair Dr. Benjamin Movsas, a radiation oncologist at

Continued on following page

VITALS

Key clinical point: Thoracic radiotherapy should be offered in addition to prophylactic cranial irradiation to patients with extensive small cell lung cancer that responds to chemotherapy.

Major finding: Patients who received thoracic radiation had significantly better 2-year overall survival (13% vs. 3%, P = .004).

Data source: A phase III randomized trial involving 498 patients with extensive small cell lung cancer who had a response to chemotherapy.

Disclosures: Dr. Slotman disclosed no relevant conflicts of interest.

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Henry Ford Hospital in Detroit.

"That's an excellent point. The dose was chosen on the safe side – 10 times 3 Gy – and was given without much toxicity, so I think the next step would be to move … to a higher dose, perhaps 15 times 3 Gy," Dr.

Thoracic radiotherapy – 30 Gy in 10 fractions – improves overall survival, progression-free survival, and intrathoracic control.

Slotman replied. The findings also support use of radiation therapy to manage other sites of metastases. "I think this study really shows that if you give local treatment to this group of patients with disseminated disease, that you are still able to make a great impact," he maintained.

In this patient population, prophylactic cranial irradiation alone reduces the risk of symptomatic brain metastases and improves overall survival, he noted, giving some background to the trial (N. Engl. J. Med. 2007;357:664-72). The large majority of patients, however, have persistent intrathoracic disease (76%) and experience intrathoracic progression (89%).

Patients from the Netherlands, United Kingdom, Norway, and Belgium were eligible for the phase III trial, known as the Chest Radiotherapy Extensive Stage Trial (CREST), if they had extensive-stage small cell lung cancer (disease beyond the hemithorax, hilar, mediastinal, and supraclavicular nodes) and had experienced a complete, partial, or good response to platinum-based chemotherapy. Additionally, they could not have any brain, leptomeningeal, or pleural metastases and could not have previously received radiation therapy to the thorax or brain.

The 498 patients were randomized evenly to receive thoracic radiation or no thoracic radiation. All received prophylactic cranial irradiation.

Overall survival curves for the two groups first began to diverge at about 9 months, Dr. Slotman noted.

Thoracic radiation was associated with a trend toward better 1-year overall survival (33% vs. 28%; hazard ratio, 0.84; $P = .066$) and significantly better 2-year overall survival (13% vs. 3%, $P = .004$), according to results reported at the meeting and simultaneously published online (Lancet 2014 Sept. 14 [doi:10.1016/S0140-6736(14)61085-0]).

Subgroup analyses suggested that thoracic radiation was similarly efficacious regardless of a variety of disease, clinical, and demographic characteristics, except for possibly having less benefit in patients who had had a complete response to chemotherapy and in patients who did not have intrathoracic disease, he said.

Thoracic radiation also was associated with better progression-free survival (HR, 0.73; $P = .001$).

The rate of intrathoracic progression was significantly lower in the thoracic radiation group as well, regardless of whether this applied to intrathoracic progression events overall (44% vs. 80%), to those that were the first site relapse (42% vs. 78%), or to those that were the only site of relapse (20% vs. 46%), Dr. Slotman reported.

The thorax was the leading site of first relapse in the control group. In contrast, sites outside the thorax and brain were most often the site of first relapse in the thoracic radiation group.

About 8% of patients overall experienced grade 3 or worse toxicity, with no significant difference between groups in the rate or nature of the events.

Dr. Slotman disclosed no relevant conflicts of interest.

VIEW ON THE NEWS

Dr. Lary Robinson, FCCP, comments: The use of radiation therapy in small cell carcinoma of the lung has been generally reserved for the relatively few patients (about 25%) presenting with limited-stage disease (cancer limited to the thorax that can be encompassed in a single radiation field). However, in this recent randomized, stage III trial of 498 patients from multiple centers in Europe, extensive (disseminated)-stage small cell lung cancer patients were treated with intermediate-dose (30 Gy) thoracic radiation to the major bulk of tumor. Remarkably, this low-toxicity palliative radiation had a significant favorable impact in 2-year overall survival (13% vs. 3%) and progression-free survival, compared with chemotherapy alone.

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