“Having a mutation of some kind that is actionable is very common in adenocarcinoma,” said Dr. Mark G. Kris, FCCP.

Lung Cancer Rx Guided By Mutation Testing

BY PATRICE WENDLING
Elsvier Global Medical News

CHICAGO – The newly minted Lung Cancer Mutation Consortium detected a driver mutation in 54% of lung adenocarcinoma tumors, allowing clinicians to use the information in real time to select erlotinib as initial therapy or to direct patients to trials targeting their specific mutation.

The collaborative effort points to the revolutionary changes taking place in the management of lung adenocarcinoma and the potential for personalized treatment in routine practice.

“While an individual mutation may be quite rare, having a mutation of some kind that is actionable is very common in adenocarcinoma,” said Dr. Mark G. Kris, FCCP, who presented the findings at the annual meeting of the American Society of Clinical Oncology (ASCO).

Earlier this year, the National Comprehensive Cancer Network and ASCO recommended epidermal growth factor receptor (EGFR) mutation testing to identify patients with advanced non-small-cell lung cancer (NSCLC) who may benefit from EGFR tyrosine kinase inhibitors such as erlotinib (Tarceva) and gefitinib (Iressa). Adenocarcinoma is the most common form of NSCLC, accounting for up to 50% of cases in the United States.

Dr. Kris said new mutations can be quickly added to the testing process and that the scope of the consortium when federal funding ends for the National Cancer Institute–sponsored initiative made up of 14 cancer centers across the country.

“I think this can serve as a model for other institutions developing similar programs in lung cancer and for other cancers,” said Dr. Kris, chief of thoracic oncology at Memorial Sloan-Kettering Cancer Center in New York.

See Lung Cancer • page 4

Sleep Debt Takes Toll in Many Aspects of Life

ADHD, weight, relationships affected.

BY DIANA MAHONEY
Elsvier Global Medical News

MINNEAPOLIS – The effects of insufficient shut-eye extend across multiple domains, according to a collection of independent studies presented at this year’s annual meeting of the Associated Professional Sleep Societies.

For example, sleep loss was linked to the development or exacerbation of symptoms of ADHD in early childhood, an individual’s genetic risk of obesity, inhibitory response to images of high-calorie foods, and even marital discontent.

ADHD and Sleep Loss

In a study designed to tease out the complex relationship between sleep problems—particularly falling asleep and staying asleep—and the development or worsening of inattention and hyperactivity in children and adolescents diagnosed with ADHD, Erika Gaylor, Ph.D., of SRI International in Menlo Park, Calif., and her colleagues analyzed data from the preschool and kindergarten waves of the Early Childhood Longitudinal Study–Birth Cohort. The cohort comprises a representative sample of approximately 6,860 children and their families living in the United States.

The investigators calculated total nighttime sleep duration based on parent-reported bedtime and wake time, and assessed children’s behavior using brief measures of attention and task persistence. Dr. Gaylor reported, “We performed two sets of regression analyses to identify whether sleep duration in preschool-age children predicts attention and hyperactivity at kindergarten entry and [whether] attention and hyperactivity symptoms at kindergarten entry predict total nighttime sleep duration.”

See Toll • page 20

Kids’ Empyema Resolves by 6 Months

BY BRUCE JANCIN
Elsvier Global Medical News

What can you tell parents they can reasonably expect after their child with empyema gets discharged from the hospital?

Clinically important sequelae commonly persist in the first month after discharge but resolve in almost all cases by 6 months. And the rare patient who has lingering significant abnormalities on chest x-ray or spirometry 6 months after leaving the hospital can expect them to normalize by 1 year, according to a prospective Canadian study.

“Long-term [sequelae] are uncommon. This information may aid decision making for clinicians and families balancing the risks and benefits of interventions,” Dr. Eyal Cohen observed.

The findings in this observational study take on added clinical relevance because the incidence of complicated pneumonia, or empyema, is increasing throughout the world, particularly in younger children.

See Empyema • page 13

Have a QR code app? Use your smartphone to view videos from major medical meetings.
IASLC Embraces CT Screening of Heavy Smokers

BY MITCHEL L. ZOLER

Elsevier Global Medical News

AMSTERDAM – The International Association for the Study of Lung Cancer has issued a call for physicians to discuss lung cancer screening with patients who match the high-risk smoking history of the people enrolled in the landmark National Lung Screening Trial.

The National Lung Screening Trial (NLST) showed that an annual, low-dose CT chest scan can lead to significant reductions in lung cancer deaths and overall mortality in patients aged 55 to 74 years who smoked for at least 30 pack-years and, if former smokers, quit within the prior 15 years (N. Engl. J. Med. 2011 [doi: 10.1056/NEJMoA1102873]).

Based on these unprecedented findings, the International Association for the Study of Lung Cancer (IASLC)’s position-writing committee issued a call for physicians to discuss the data and its implications with such patients.

“It is appropriate for heavy smokers ages 55 to 74 to discuss relevant lung cancer screening information with their physicians to assist them in deciding whether to undergo spiral CT screening,” said the statement, issued as IASLC started its world conference.

Although some committee members, including the chairman, urged caution when routinely discussing screening with the target population before the cost-effectiveness of this approach is proven, two of the Americans on the 10 member position-statement writing committee endorsed immediately offering screening to fully informed people who match the study’s screening profile.

“For patients with metastatic lung cancer, the cure rate is essentially zero. Finding lung cancer early is the best way to deal with this disease, and that’s why this is such an extraordinary result,” said Dr. Roy S. Herbst, another member of the statement-writing committee and chief of medical oncology at Yale University in New Haven, Conn.

“Even with all the cautions, I think that in the United States at least you’ll see widespread adoption of [CT] screening largely sponsored by the National Cancer Institute. Assuming that the CMS [Centers for Medicare and Medicaid Services] and insurers will pick up these costs, I think [screening] is something we’re going to see. I think there will be great pressure in the United States for this to be covered, at a cost of about $300-$400 per scan.

“At Yale, we’ll start screening people who meet the enrollment criteria for the trial, as will several other U.S. centers. We’ll offer screening with all the caveats,” including informing patients about the risks they will face from screening, their need to stop smoking, their need for ongoing screening, and the need to have a multidisciplinary team in place at the screening site to deal with all the possible consequences of screening. Dr. Herbst said at the World Conference on Lung Cancer.

“We know there is effectiveness from screening, but is there cost effectiveness? Is there value?” asked Dr. Richard Gralla, another member of the statement-writing committee and chief of hematology-oncology at North Shore University Medical Center and Long Island Jewish Medical Center in New Hyde Park, N.Y.

“My prediction is that screening will not only be shown to be cost effective, but it will be very cost effective. It will also be very expensive to run annual screens on the millions of middle-aged smokers who meet the trial’s screening profile, he added. The NLST report estimated that 7 million Americans match the age and smoking history of the people enrolled in the trial.

“By thrusting medicine into a new era of routine lung cancer screening, these developments will trigger creation of a new system of quality oversight for lung cancer screening that will likely follow the model of breast cancer screening.”

“There is a laundry list of requirements that will need to be established by the institutions that want to do CT screening,” said Dr. Denise R. Aberle, professor of radiology at the University of California, Los Angeles, and a collaborator on the NLST. “That will likely evolve into a form of accreditation to better guarantee quality assurance, as with breast cancer screening.”

“Dr. Aberle also noted that the NLST researchers collected cost-effectiveness data, and that they will soon release a report on their analysis of those data. Routine lung cancer screening will also place new responsibilities on the thoracic surgeons who follow up on suspicious lung lesions found though screening, most of which will not be cancers.

“For surgeons it will be a very large challenge to offer correct treatment to patients with very small cancers,” said Dr. Jesper Pedersen, a thoracic surgeon at Copenhagen University Hospital. “We’re planning on writing guidelines for surgeons, because they will be at risk by operating on so many patients without lung cancer.”

“The NLST results showed that 96% of suspicious lesions identified by CT screening were not cancers.

“There is potential for physical and psychiatric harm from cancer screening, but the results from many studies of breast cancer screening have shown that the benefits of screening outweigh its harms,” said David R. Gandara, IASLC president and professor of medicine and director of the thoracic oncology program at the University of California, Davis, in Sacramento.

“We’re in the early days of screening for lung cancer, and we must do everything to make sure that screening is done appropriately and that follow-up is appropriate. But our message to patients about screening is positive. We can’t overemphasize that,” Dr. Gandara said.

Dr. Herbst said that he has been a consultant to, on the advisory boards of, and received research grants from several pharmaceutical companies, including Genentech, Boehringer Ingelheim, Sanofi-Aventis, Pfizer, and ImClone. Dr. Gralla and Dr. Aberle had no relevant disclosures. Dr. Pedersen said that he has been on the speakers bureau for Eli Lilly and Roche and received grant support from AstraZeneca. Dr. Gandara said that he has been a consultant to or received research support from several pharmaceutical companies, including AstraZeneca, GlaxoSmithKline, Genentech, Merck, and Novartis.

CHEST PHYSICIAN

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CHEST PULMONARY MEDICINE

PULMONARY MEDICINE

AUGUST 2011 • CHEST PHYSICIAN
CT Lung Cancer Screening Raises Policy Questions

BY KERRI WACHTER
Elsevier Global Medical News

Final results ... of the findings of the NLST, the current NLST data alone are, in our opinion, insufficient to fully inform such important decisions.

They noted that “the observation that low-dose CT screening can reduce the rate of death from lung cancer has generated many questions.” Among these they listed: Will populations with different risk profiles benefit from screening? Could less-frequent screening programs be equally effective? Would the use of different criteria for a positive screening result translate to similar benefit? For how long should people be screened?

In an editorial, Dr. Harold C. Sox, professor of medicine at the Dartmouth Institute in Hanover, N.H., agreed with the investigators’ reservations. In particular, “policy makers should wait for cost-effectiveness analyses to determine the amount of overdiagnosis in the NLST and, perhaps, identification of biologic markers of cancers that do not progress.”

In addition, “it may be possible to define subgroups of smokers who are at higher or lower risk for lung cancer and tailor the screening strategy accordingly,” he said. “The findings of the NLST regarding lung-cancer mortality signal the beginning of the end of one era of research on lung-cancer screening and the start of another. The focus will shift to informing the difficult patient-centered and policy decisions that are yet to come.”

Dr. Sox also noted that “overdiagnosis is a problem because predicting which early-stage cancers will not progress is impossible. To de-

VATS, Open Lobectomy Similar for Early Lung Cancer

BY MITCHEL L. ZOLER
Elsevier Global Medical News

AMSTERDAM – Video-assisted thoracoscopic surgery worked as well as open lobectomy for 5-year survival in early-stage lung cancer, based on a secondary analysis of a randomized trial that recruited patients who underwent surgery as part of a multicenter trial.

“VATS [video-assisted thoracoscopic surgery] is a considerable alternative to open lobectomy for early-stage lung cancer,” said Dr. Walter J. Scott, FCCP, at the World Conference on Lung Cancer. He stressed that the study included only patients with early-stage lung cancer that was node-negative or was non-nodular N1 disease, and the selection criteria of early-stage cancer were not specific for these patients. Until now, questions existed about the oncologic efficacy of VATS, noted Dr. Scott, chief of the division of thoracic surgery at Fox Chase Cancer Center in Philadelphia. But “VATS lobectomy provides comparable oncologic outcomes” for this group of patients, he said.

His team used data collected from 964 lung cancer patients who participated in a multicenter study during 1999–2004 that compared two different strategies for lymph node assessment in early-stage lung cancer (Ann Thorac Surg. 2006; 81:1013-20). Although most surgeons did not perform VATS during this time, a few surgeons did, and 5-year outcome results were available for 66 patients in the study undertaken VATS.

VATS and Open Lobectomy Compared (5-year risk-adjusted measures)

Patients who had VATS (n = 66)

71.6%

83.9%

Local disease-free survival

89.4%

92.6%

Freedom from new primary tumors

HR = 1.19

HR = 0.70

HR = 1.66

HR = 1.57

HR = 0.65

HR = 0.71

HR = 0.66

HR = 0.69

Local disease-free survival

75.2%

66.2%

Overall survival

69.9%

71.8%

Survival, local disease-free survival, or freedom from new primary tumors (see table). Dr. Scott reported at the meeting, which was sponsored by the International Association for the Study of Lung Cancer.

Dr. Scott said that he is a shareholder in Biogen Idec, Celgene, and Johnson & Johnson.
**Trial Upholds Erlotinib Use in EGFR-Mutant Lung Cancer**

**The objective response rate was 58% for erlotinib vs. 15% for chemotherapy.**

**By Patrice Wendling**

Elsevier Global Medical News

CHICAGO — Data from the prospective, phase III EURTAC trial cement the need for personalized treatment of lung cancer patients but also leave clinicians in uncharted waters in terms of treatment options.

First-line erlotinib (Tarceva) improved the primary end point of progression-free survival from 5.2 months with standard platinum-based chemotherapy to 9.4 months in white patients who had advanced non–small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutations, in an interim analysis.

Study cochair Dr. Rafael Rosell, president of the Spanish Lung Cancer Group, reported a significant 63% reduction in the risk of progression (hazard ratio, 0.37; log-rank P < .0001) in an updated analysis presented at the annual meeting of the American Society of Clinical Oncology.

Based on positive results in the earlier interim analysis, Genentech and partner OSI Pharmaceuticals announced in January that the trial had been halted and they were set to pursue a broader indication for erlotinib as first-line treatment in NSCLC with EGFR mutations.

Erlotinib, a tyrosine kinase inhibitor (TKI), is approved in the United States and Europe as a maintenance and second-line treatment for advanced or metastatic NSCLC with and without EGFR-activating mutations. Genentech’s parent company, Roche, submitted a bid to the European Medicines Agency in June 2010 to expand the drug’s label.

Even though the proverbial cat had already been let out of the bag by the drug makers, EURTAC caused a stir at ASCO, where the full data were formally presented and the study was chosen as one of the Best of ASCO 2011.

Invited discussant Dr. Tony Mok, of the Chinese University of Hong Kong called the data trustworthy and a true reflection of erlotinib’s efficacy in patients with EGFR mutations. He drew parallels between EURTAC and the OPTIMAL trial in which erlotinib proved potent among Asians with this genetically distinct form of lung cancer. EGFR mutations were present in about 8% of patients in the West and about 30% of Asians, and they are associated with an increased response to erlotinib and the TKI gefitinib (Iressa).

Dr. Mok said that there’s a good chance erlotinib will be approved as first-line therapy. The EURTAC data are on par with the IPASS trial that helped gain approval for gefitinib as first-line therapy for patients with EGFR mutations in more than 70 countries, except the United States, where gefitinib use is restricted, and AstraZeneca has said it will not seek a new indication for the drug. “Now we have two drugs,” said Dr. Mok, principal investigator of IPASS. “What are we going to do when faced with an EGFR mutation? Is there a difference in terms of the effectiveness between the [tyrosine kinase inhibitors] in patients with EGFR mutations?”

**IS THERE A DIFFERENCE IN TERMS OF THE EFFECTIVENESS BETWEEN THE [TYROSINE KINASE INHIBITORS] IN PATIENTS WITH EGFR MUTATIONS?**

The EURTAC trial randomly assigned 174 Chinese-naïve, stage IIIB/IV NSCLC patients with exon 19 deletions or L858R mutations to receive erlotinib 150 mg/day alone or platinum-based chemotherapy every 3 weeks for 4 cycles. The doublet could include cisplatin 75 mg/m² on day 1 plus docetaxel 75 mg/m² on day 1; cisplatin 75 mg/m² on day 1 plus gemcitabine 1,250 mg/m² on days 1 and 8; or carboplatin area under the curve (AUC) 5 on day 1 plus docetaxel 75 mg/m² on day 1 or carboplatin AUC 5 on day 1 plus gemcitabine 1,000 mg/m² on days 1 and 8.

The objective response rate was 58% for erlotinib vs. 15% for chemotherapy in the updated analysis, said Dr. Rosell, head of medical oncology at the Catalan Institute of Oncology in Barcelona. At the time of the interim analysis, two patients had a complete response to erlotinib and 40 had partial responses, with 8 additional partial responses reported in the updated analysis. No patient had a complete response with chemotherapy, eight patients had partial response to erlotinib, and five more reported partial responses in the updated analysis.

The disease control rate in the interim analysis was 79% for erlotinib vs. 66% for chemotherapy. Median overall survival was 18.8 months with chemotherapy and 22.9 months in the interim analysis (hazard ratio, 0.80; log-rank P = .42). As of the Jan. 26, 2011, cutoff date for the updated analysis, 94 patients remain in overall survival follow-up, with a high level of known crossover, Dr. Rosell said. A subgroup analysis suggested that progression-free survival was better in patients with a performance status of 0, never-smokers, and those with an exon 19 deletion.

The majority of patients who relapsed on erlotinib were switched to chemotherapy. The chemotherapeutic activity of erlotinib was consistent with previous studies, he noted.

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**Testing Directed Therapy**

Lung Cancer • from page 1

A total of 1,234 patients with stage IV lung adenocarcinoma agreed to undergo testing for 10 known mutations using standard multiplexed assays and fluorescence in situ hybridization. Inadequate tissue was obtained in 170 patients (14%) in a study group of 1,064 patients. Mutations were identified in 280 (54%) of 516 tumor specimens tested to date (95% confidence interval 50%-59%).

As suspected, the most common mutations were KRAS (22%), EGFR (17%), and EML4-ALK rearrangement (7%). Dr. Kris said. Other mutations were BRAF (2%), PIK3CA, HER2, MET amplification, MEK1, NRAS, and AKT1.

The vast majority (97%) of mutations were mutually exclusive. Of the 14 double-mutant tumors, the two molecular lesions most commonly seen together were MET amplification and PIK3CA, he said. Four sites had testing available prior to the study, with seven additional patients now able to provide multiplex mutation testing. Preliminary data from 121 patients enrolled at a single site show that driver mutations were found in 60 (50%) of 122 patients in whom testing was completed. That information was used to direct therapy in 39 patients — 19 to receive erlotinib upfront and 16 to go on a trial of an agent targeting their specific mutation.

“In truth, we used it for every patient because when we did not find an EGFR mutation, we did not give them erlotinib,” Dr. Kris said.

The turnaround time for mutational testing varied by site, but generally took only a few days. The great majority of time is in specimen acquisition, preparation, and submission to the molecular lab.

Those are formidable obstacles that we all have to face,” Dr. Kris said. “But I think with progression, we’ll get over those.”

Invited discussant Dr. Masawamy Govindan, professor of medicine at Washington University in St. Louis, said EGFR mutation testing is ready for routine clinical use and that EML4 ALK fusion testing will soon be ready. He pointed out that with more than 13,000 NSCLC mutations alone in the Catalog of Somatic Mutations in Cancer database and that many questions remain, including the role of the effectiveness of mutational testing.

“It’s important to remember that not all mutations are created equal,” he said. Dr. Govindan described the most important aspect of the presentation as the linking of the consortium to targeted clinical trials. Last year he was

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**IN TRUTH, WE USED [TEST RESULTS] FOR EVERY PATIENT BECAUSE WHEN WE DID NOT FIND AN EGFR MUTATION, WE DID NOT GIVE THEM ERLOTINIB.**

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**VITALS**

**Major Finding:** Erlotinib resulted in a significant 63% reduction in the risk of progression, compared with standard chemotherapy (HR 0.37).

**Data Source:** Phase III, prospective randomized EURTAC trial in 174 white patients with advanced non-small cell lung cancer and EGFR mutations.

**Disclosures:** The Spanish Lung Cancer Group sponsored the trial. Dr. Rosell disclosed a consultant/advisory role with Roche. Two of his coauthors reported a similar role, with one also providing expert testimony for Roche. Dr. Mok disclosed relationships with several drug companies, including AstraZeneca, Roche, Boehringer Ingelheim, and Pfizer.

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For the treatment of adults with community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible bacteria, as indicated below

An IV Cephalosporin for

COMMUNITY-ACQUIRED BACTERIAL PNEUMONIA
CABP

AND

ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS
ABSSSI

INDICATIONS
- TEFLARO® is indicated for the treatment of community-acquired bacterial pneumonia (CABP) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: Streptococcus pneumoniae (including cases with concurrent bacteremia), Staphylococcus aureus (methicillin-susceptible isolates only), Haemophilus influenzae, Klebsiella pneumoniae, Klebsiella oxytoca, and Escherichia coli.
- TEFLARO is also indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: Staphylococcus aureus (including methicillin-susceptible and -resistant isolates), Streptococcus pyogenes, Streptococcus agalactiae, Escherichia coli, Klebsiella pneumoniae, and Klebsiella oxytoca.

IMPORTANT SAFETY INFORMATION
- Contraindications
  - TEFLARO is contraindicated in patients with known serious hypersensitivity to ceftaroline or other members of the cephalosporin class. Anaphylaxis and anaphylactoid reactions have been reported with ceftaroline.

Please see additional Important Safety Information throughout and brief summary of Prescribing Information on last page of this advertisement. Please also see full Prescribing Information at www.TEFLARO.com.
INDICATIONS AND USAGE

- **TEFLARO** is indicated for the treatment of **community-acquired bacterial pneumonia (CABP)** caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Streptococcus pneumoniae* (including cases with concurrent bacteremia), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Escherichia coli*.

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To reduce the development of drug-resistant bacteria and maintain the effectiveness of **TEFLARO** and other antibacterial drugs, **TEFLARO** should be used to treat only ABSSSI or CABP that are proven or strongly suspected to be caused by susceptible bacteria.

IMPORTANT SAFETY INFORMATION

**Warnings and Precautions**

Hypersensitivity Reactions

- Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and serious skin reactions have been reported with beta-lactam antibacterials. Before therapy with **TEFLARO** is instituted, careful inquiry about previous hypersensitivity reactions to other cephalosporin-penicillins, or carbapenems should be made. If this product is to be given to a penicillin- or other beta-lactam-allergic patient, caution should be exercised because cross sensitivity among beta-lactam antibacterial agents has been clearly established.

- If an allergic reaction to **TEFLARO** occurs, the drug should be discontinued. Serious acute hypersensitivity (anaphylactic) reactions require emergency treatment with epinephrine and other emergency measures that may include airway management, oxygen, intravenous fluids, antihistamines, corticosteroids, and vasopressors as clinically indicated.

**Clostridium difficile-associated Diarrhea**

- *Clostridium difficile*-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial agents, including **TEFLARO**, and may range in severity from mild diarrhea to fatal colitis. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents. If CDAD is suspected or confirmed, antibacterials not directed against *C. difficile* should be discontinued, if possible.
Bactericidal Activity Against a Broad Spectrum of Gram-positive and Gram-negative Pathogens, Including *S. pneumoniae* in CABP and MRSA in ABSSSI

Proven efficacy in 2 common infections in patients admitted to the hospital

- **CABP**
- **ABSSSI**

- Convenient q12h dosing in CABP and ABSSSI
  - 600 mg intravenous over 1 hour
  - Treatment duration
    - 5-7 days for CABP
    - 5-14 days for ABSSSI

**IMPORTANT SAFETY INFORMATION**

**Direct Coombs’ Test Seroconversion**
- Seroconversion from a negative to a positive direct Coombs’ test result occurred in 120/1114 (10.8%) of patients receiving TEFLARO and 49/1116 (4.4%) of patients receiving comparator drugs in the four pooled Phase 3 trials. No adverse reactions representing hemolytic anemia were reported in any treatment group. If anemia develops during or after treatment with TEFLARO, drug-induced hemolytic anemia should be considered. If drug-induced hemolytic anemia is suspected, discontinuation of TEFLARO should be considered and supportive care should be administered to the patient if clinically indicated.

**Development of Drug-Resistant Bacteria**
- Prescribing TEFLARO in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Please see additional Important Safety Information throughout and brief summary of Prescribing Information on last page of this advertisement.
TEFLARO CABP Study Designs\(^1,3\)

**Type of trial:** Two randomized, multicenter, multinational, double-blind, noninferiority trials

**Study population:** 1231 adults with a diagnosis of CABP

**Comparative agents:**
- TEFLARO – 600 mg administered IV over 1 hour every 12 hours for 5-7 days;
- Ceftriaxone – 1 g ceftriaxone administered IV over 30 minutes every 24 hours for 5-7 days

**Adjunctive therapy:**
- CABP Trial 1, two doses on Day 1 of oral clarithromycin 500 mg every 12 hours;
- CABP Trial 2, no adjunctive macrolide therapy

### TEFLARO CABP Study Populations

<table>
<thead>
<tr>
<th>Test of Cure (TOC) Populations(^†)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MITT</strong></td>
<td>Modified Intent-to-treat All randomized subjects who received any amount of study drug.</td>
</tr>
<tr>
<td><strong>MITTE</strong></td>
<td>Modified Intent-to-treat Efficacy All subjects in the MITT population who were in PORT Risk Class III or IV at baseline.</td>
</tr>
<tr>
<td><strong>CE</strong></td>
<td>Clinically Evaluable All subjects in the MITTE population who demonstrated sufficient adherence to the protocol. Sufficient adherence is defined as patients who met the minimal disease criteria for CABP and for whom sufficient information regarding the CABP was available to determine the patient’s outcome.</td>
</tr>
<tr>
<td><strong>ME</strong></td>
<td>Microbiologically Evaluable All subjects in the CE population who had at least one typical bacterial pathogen identified at baseline from an appropriate microbiological specimen (eg, blood, sputum, or pleural fluid).</td>
</tr>
</tbody>
</table>

*To evaluate the treatment effect of ceftaroline, an analysis was conducted in CABP patients for whom the treatment effect of antibiotics may be supported by historical evidence. This analysis endpoint required subjects to meet sign and symptom criteria at Day 4 of therapy: a responder had to both (a) be in stable condition according to consensus treatment guidelines, and (b) show improvement from baseline on at least one symptom of cough, dyspnea, pleuritic chest pain, or sputum production, while not worsening on any of these four symptoms.

\(^†\)The protocol-specified analyses included clinical cure rates at the TOC (8 to 15 days after the end of therapy) in the coprimary MITTE and CE populations and clinical cure rates at TOC by pathogen in the ME population.

### INDICATION AND USAGE

- **TEFLARO** is indicated for the treatment of community-acquired bacterial pneumonia (CABP) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Streptococcus pneumoniae* (including cases with concurrent bacteremia), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Escherichia coli*.
- To reduce the development of drug-resistant bacteria and maintain the effectiveness of TEFLARO and other antibacterial drugs, TEFLARO should be used to treat only CABP that is proven or strongly suspected to be caused by susceptible bacteria.

### IMPORTANT SAFETY INFORMATION

#### Adverse Reactions

- In the four pooled Phase 3 clinical trials, serious adverse events occurred in 98/1300 (7.5%) of patients receiving TEFLARO and 100/1297 (7.7%) of patients receiving comparator drugs. Treatment discontinuation due to adverse events occurred in 35/1300 (2.7%) of patients receiving TEFLARO and 48/1297 (3.7%) of patients receiving comparator drugs with the most common adverse events leading to discontinuation being hypersensitivity for both treatment groups at a rate of 0.3% in the TEFLARO group and 0.5% in the comparator group.
- No adverse reactions occurred in greater than 5% of patients receiving TEFLARO. The most common adverse reactions occurring in >2% of patients receiving TEFLARO in the pooled Phase 3 clinical trials were diarrhea, nausea, and rash.

Please see additional Important Safety Information throughout and brief summary of Prescribing Information on last page of this advertisement.
TEFLARO Demonstrated Clinical Response at Day 4 (mITT) in Community-Acquired Bacterial Pneumonia

<table>
<thead>
<tr>
<th></th>
<th>Clinical response, % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TEFLARO</strong></td>
<td>69.6% (48/69)</td>
</tr>
<tr>
<td><strong>Ceftriaxone</strong></td>
<td>58.3% (42/72)</td>
</tr>
</tbody>
</table>

Treatment Difference 11.2 (95% CI: -4.6, 26.5)

Neither trial established that TEFLARO was statistically superior to ceftriaxone in terms of clinical response rates.

TEFLARO Demonstrated Efficacy at TOC (CE) in Community-Acquired Bacterial Pneumonia

<table>
<thead>
<tr>
<th></th>
<th>Clinical cure rates, % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TEFLARO</strong></td>
<td>86.6% (194/224)</td>
</tr>
<tr>
<td><strong>Ceftriaxone</strong></td>
<td>78.2% (183/234)</td>
</tr>
</tbody>
</table>

Treatment Difference 8.4 (95% CI: 1.4, 15.4)

Treatment Difference 5.2 (95% CI: -2.2, 12.8)

Neither trial established that TEFLARO was statistically superior to ceftriaxone in terms of clinical response rates.

PATIENTS WITH KNOWN OR SUSPECTED MRSA WERE EXCLUDED FROM BOTH TRIALS.

*FOCUS = Ceftraxone Community-Acquired Pneumonia Trial vs Ceftriaxone in Hospital Patients. FOCUS 1 = CABP Trial 1, FOCUS 2 = CABP Trial 2.

†There are insufficient historical data to establish the magnitude of drug effect for antibacterial drugs compared with placebo at a TOC time point. Therefore, comparisons of TEFLARO to ceftriaxone based on clinical response rates at TOC cannot be utilized to establish noninferiority.

IMPORTANT SAFETY INFORMATION

**Drug Interactions**

- No clinical drug-drug interaction studies have been conducted with TEFLARO.
- There is minimal potential for drug-drug interactions between TEFLARO and CYP450 substrates, inhibitors, or inducers; drugs known to undergo active renal secretion; and drugs that may alter renal blood flow.
## TEFLARO ABSSSI Study Design

<table>
<thead>
<tr>
<th>Type of trial:</th>
<th>Two identical, randomized, multicenter, multinational, double-blind, noninferiority trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study population:</td>
<td>1396 adults with clinically documented complicated skin and skin structure infection</td>
</tr>
<tr>
<td>Comparative agents:</td>
<td>TEFLARO – 600 mg administered IV over 1 hour every 12 hours for 5-14 days; Vancomycin plus aztreonam — 1 g vancomycin administered IV over 1 hour followed by 1 g aztreonam administered IV over 1 hour every 12 hours for 5-14 days</td>
</tr>
<tr>
<td>Treatment duration:</td>
<td>Treatment duration was 5 to 14 days. A switch to oral therapy was not allowed</td>
</tr>
</tbody>
</table>

### TEFLARO Study Populations

<table>
<thead>
<tr>
<th>Day 3 Population*</th>
<th>The analysis evaluated patients with lesion size ≥75 cm² and having one of the following infection types:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>– Major abscess with ≥5 cm of surrounding erythema</td>
</tr>
<tr>
<td></td>
<td>– Wound infection</td>
</tr>
<tr>
<td></td>
<td>– Deep/extensive cellulitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test of Cure (TOC) Populations†</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MITT Modified Intent-to-treat</td>
<td>All randomized subjects who received any amount of study drug</td>
</tr>
<tr>
<td>CE Clinically Evaluable</td>
<td>Patients in the MITT population who demonstrated sufficient adherence to the protocol. Sufficient adherence is defined as patients who met the minimal clinical disease criteria for cSSSI and all evaluable criteria, including subjects who received at least the pre-specified minimal amount of the intended dose and duration of study drug therapy, for which sufficient information regarding the cSSSI site is available to determine the subject’s outcome, and for which there were no confounding factors that interfered with the assessment of that outcome.</td>
</tr>
<tr>
<td>ME Microbiologically Evaluable</td>
<td>This population consists of a subset of subjects from the CE population who had at least one bacterial pathogen identified from a blood culture or culture of an adequate microbiological sample obtained from the cSSSI site at baseline and who had susceptibility testing performed on at least one of the isolated baseline pathogens.</td>
</tr>
</tbody>
</table>

*To evaluate the treatment effect of ceftaroline, an analysis was conducted in 797 patients with ABSSSI (such as deep/extensive cellulitis or a wound infection [surgical or traumatic]) for whom the treatment effect of antibacterials may be supported by historical evidence. This analysis evaluated responder rates based on achieving both cessation of lesion spread and absence of fever on Trial Day 3.
†The protocol-specifi ed analyses included clinical cure rates at the TOC (8 to 15 days after the end of therapy) in the coprimary CE and MITT populations and clinical cure rates at TOC by pathogen in the ME population.

## INDICATION AND USAGE

- **TEFLARO** is indicated for the treatment of **acute bacterial skin and skin structure infections (ABSSSI)** caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*.

- To reduce the development of drug-resistant bacteria and maintain the effectiveness of **TEFLARO** and other antibacterial drugs, **TEFLARO** should be used to treat only **ABSSSI** that is proven or strongly suspected to be caused by susceptible bacteria.

## IMPORTANT SAFETY INFORMATION

### Use in Specific Populations

- **TEFLARO** has not been studied in pregnant women. Therefore, **TEFLARO** should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.
- It is not known whether ceftaroline is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when **TEFLARO** is administered to a nursing woman.
- Safety and effectiveness in pediatric patients have not been established.
- Because elderly patients, those ≥65 years of age, are more likely to have decreased renal function and ceftaroline is excreted primarily by the kidney, care should be taken in dose selection in this age group and it may be useful to monitor renal function. Dosage adjustment for elderly patients should therefore be based on renal function.
- Dosage adjustment is required in patients with moderate (CrCl >30 to ≤50 mL/min) or severe (CrCl ≥15 to ≤30 mL/min) renal impairment and in patients with end-stage renal disease (CrCl <15 mL/min).
- The pharmacokinetics of ceftaroline in patients with hepatic impairment have not been established.
**ABSSSI**

**TEFLARO Demonstrated Clinical Response at Day 3 in Acute Bacterial Skin and Skin Structure Infections**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Clinical responders, % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEFLARO monotherapy</td>
<td>74.0% (148/200)</td>
</tr>
<tr>
<td>Vancomycin + aztreonam</td>
<td>64.6% (135/209)</td>
</tr>
</tbody>
</table>

Treatment Difference 9.4 (95% CI: 0.4, 18.2)

Neither trial established that TEFLARO was statistically superior to vancomycin plus aztreonam in terms of clinical response rates.

**ABSSSI**

**TEFLARO Demonstrated Efficacy at TOC (CE) in Acute Bacterial Skin and Skin Structure Infections**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Clinical cure rates, % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEFLARO monotherapy</td>
<td>91.1% (288/316)</td>
</tr>
<tr>
<td>Vancomycin + aztreonam</td>
<td>93.3% (280/300)</td>
</tr>
</tbody>
</table>

Treatment Difference 2.2 (95% CI: -6.6, 2.1)

Neither trial established that TEFLARO was statistically superior to vancomycin plus aztreonam in terms of clinical response rates.

*CANVAS= Ceftaroline vs Vancomycin in Skin and Skin Structure Infection. CANVAS 1=ABSSSI Trial 1, CANVAS 2=ABSSSI Trial 2.

1There are insufficient historical data to establish the magnitude of drug effect for antibacterial drugs compared with placebo at a TOC time point. Therefore, comparisons of TEFLARO to vancomycin plus aztreonam based on clinical response rates at TOC cannot be utilized to establish noninferiority.

**CRIZOTINIB BOOSTS OVERALL SURVIVAL IN ALK-NSCLC**

**BY MICHIEL L. ZOLER**
Elsiever Global Medical News

AMSTERDAM—Crizotinib treatment boosted overall survival of selected patients with advanced non-small cell lung cancer by about a year compared with patients on standard chemotherapy in a historical control analysis, adding to the growing body of evidence for the efficacy of this novel targeted therapy.

“Crizotinib may prolong overall survival and fundamentally alter the natural history of ALK-positive NSCLC,” Dr. Alice T. Shaw said at the World Conference on Lung Cancer. Results from several recent studies indicated that about 7% of patients with advanced NSCLC have ALK-positive tumors for which crizotinib is a targeted therapy, or crizotinib. “Continued on following pages 12a—12b"

**TEFLARO® (ceftaroline fosamil) injection for intravenous (IV) use**
Rx Only

Summary of full Prescribing Information...

**INDICATIONS AND USAGE: Teflaro® (ceftaroline fosamil) is indicated for the treatment of patients with the following infections caused by susceptible and susceptible-to-resistant microorganisms. Acute Bacterial Skin and Skin Structure Infections - Teflaro is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSIS) caused by susceptible and susceptible-to-resistant microorganisms. Staphylococcus aureus (including methicillin-resistant and -susceptible), Streptococcus pyogenes (beta-hemolytic streptococci), Streptococcus pneumoniae (including cases with and without penicillin-resistant strains), Haemophilus influenzae, Klebsiella pneumoniae, and Enterococcus faecalis. Community-Acquired Bacterial Pneumonia - Teflaro is indicated for the treatment of community-acquired pneumonia (CAP) caused by susceptible and susceptible-to-resistant strains of the following Gram-positive and Gram-negative microorganisms: Streptococcus pneumoniae (including cases with and without penicillin-resistant strains), Haemophilus influenzae, Klebsiella pneumoniae, and Enterococcus faecalis.

- To reduce the development of drug-resistant bacteria and maintain the effectiveness of Teflaro and other antibacterial drugs, Teflaro should be used only to treat infections that are caused by susceptible bacteria. Specific appropriateness for medical treatment of an infection should be reviewed in order to determine the causative pathogens and to determine their susceptibility to Teflaro. When culture and susceptibility information are available, they should guide the selection of antibacterial therapy. In the absence of such data, local epidemiology and sensitivity patterns may contribute to the empiric selection of therapy.

**CONTRAINDICATIONS:** Teflaro is contraindicated in patients with known severe hypersensitivity to any component of Teflaro or any other cephalosporins, penicillins, or lactam antibiotics.

**WARNINGS AND PRECAUTIONS: Hypersensitivity Reactions:** Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and serious skin reactions have been reported in patients receiving beta-lactam antibiotics. Before therapy with Teflaro is initiated, careful inquiry about previous hypersensitivity reactions to other cephalosporins, penicillins, or other beta-lactam antibiotics should be made. If an allergic reaction to a beta-lactam antibiotic occurs during Teflaro therapy, the drug should be discontinued. Serious acute hypersensitivity (anaphylactic) reactions require emergency treatment with epinephrine and other appropriate antiallergic measures. Early discontinuation of therapy may prevent the development of a serious reaction. The possibility of an allergic reaction to Teflaro should be considered in all patients with dermatologic symptoms following antibiotic use. Careful medical history is strongly recommended in patients with a history of drug allergy. There have been reports of severe hypersensitivity reactions occurring in patients treated with Teflaro, including those with a history of drug allergy. Symptoms that may be suggestive of anaphylactic reactions have included rash, pruritus, angioedema, wheezing, and hypotension. Life-threatening or fatal reactions have been reported rarely, including reports of status asthmaticus and urticaria. The possibility of a serious anaphylactoid reaction to Teflaro should be considered in patients with a history of drug allergy. The possibility of a severe anaphylactoid reaction to Teflaro should be considered if rash, pruritus, angioedema, wheezing, or hypotension occur following the administration of Teflaro. Because serious anaphylactic reactions have been reported rarely, including reports of status asthmaticus and urticaria, patients should be observed for at least 6 hours following the administration of Teflaro. The possibility of a severe anaphylactic reaction should be considered in patients with a history of drug allergy. If a severe anaphylactic reaction occurs, Teflaro therapy should be discontinued immediately and the patient should be treated according to recognized established guidelines.

**ADVERSE REACTIONS: The most frequent adverse reactions (incidence ≥ 5%) are:

- gastrointestinal: diarrhea, nausea, vomiting, abdominal pain, colitis, cramps, retching, acute pancreatitis, ileus, fecal incontinence, melena, elevated transaminases, incontinence, hypertransaminasemia, hematochezia, and anorexia.

- infections: osteomyelitis, cellulitis, erysipelas, endocarditis, paronychia, wound infection, vaginitis.

- renal: hypokalemia, hyperkalemia, increased creatinine, elevated BUN, hemoglobinuria, hematuria, and transient proteinuria.

- respiratory: dry cough, pharyngitis.

- skin: rash, pruritus, maculopapular rash, urticaria, angioedema, erythema, toxic epidermal necrolysis, Stevens-Johnson syndrome.

- urological: nephrolithiasis.

- miscellaneous: fever, chills, cholestatic jaundice, increased SGPT, increased alkaline phosphatase, elevated bilirubin, increased AST, increased ALT, and increased cholesterol.

**Drug-Drug Interactions:** The following drugs are likely to increase serum levels of Teflaro and therefore may result in increased adverse reactions of Teflaro:

- CYP3A4 inhibitors (e.g., azoles, ketoconazole, itraconazole, clarithromycin, indinavir, verapamil, diltiazem, and nefazodone).

- CYP2C9 inhibitors (e.g., fluconazole, midazolam).

The following drugs are likely to decrease serum levels of Teflaro and therefore may result in decreased adverse reactions of Teflaro:

- CYP2C19 inhibitors (e.g., fluvoxamine).

- CYP2C19 inducers (e.g., St. John’s wort).

**Drug-Laboratory Test Interactions:** Teflaro was not found to interfere with the following laboratory tests:

- Coagulation tests.

- Blood cell counts.

- Liver function tests.

- Prothrombin time.

- Partial thromboplastin time.

- Urinalyses.

- Serum electrolytes.

- Serum glucose.

- Serum urea nitrogen.

- Serum creatinine.

- BUN.

- HCG.

- Other pregnancy tests.

- Pregnancy confirmation tests.

**Special Populations:**

**Geriatric Use:** In clinical trials, 7% of patients were ≥ 65 years of age. Teflaro was administered to 980 patients ≥ 65 years and to 462 patients ≥ 75 years. No overall differences in safety or efficacy were observed between these older and younger patients. Because elderly patients are usually more susceptible to the adverse reactions of beta-lactam antibiotics, treatment should be administered with caution. Aged patients require careful monitoring for signs of adverse reactions, particularly in the elderly population. Because elderly patients usually have decreased renal function, in patients ≥ 65 years of age, Teflaro should be administered with a reduced dosage of 600 mg every 12 hours or 1200 mg every 24 hours, depending on the severity of the patient’s renal impairment. This dosage is the same as that of patients ≥ 18 years of age. Elderly patients ≥ 75 years of age may require lower doses, depending on their renal function. Because elderly patients are generally more susceptible to the adverse effects of antibiotics, caution should be exercised in using prophylactic therapy in the elderly.

**Pulmonary Medicine (May 2011) 12:1**

**For regulatory approval, people look at overall survival, but you’ll never get [overall survival] from the large randomized studies because it would be unethical not to let patients who were matched receive the drug (or placebo) that had been studied. People look at all-cause mortality; people look at progression-free survival at 10 months. Dr. Shaw and her associates used data in this analysis was funded by Pfizer, the company developing the drug. Dr. Shaw said that she has been a consultant to Pfizer, Ariad, Chugai, and Millennium. She has received research support from Novartis and AstraZeneca.

**ALK-positive patients do not intrinsically do better on their own, but you can make them live a longer life if you give them this targeted therapy, crizotinib,” said Dr. Shaw, an oncologist at Harvard Medical School and Massachusetts General Hospital, both in Boston. In May, the Food and Drug Administration began a priority review of crizotinib, because the company had requested approval to treat patients with advanced, ALK-positive NSCLC.
Proton Therapy May Lead to Fewer Side Effects

By Sara Freeman

LONDON—Proton beam therapy for non–small cell lung cancer is associated with fewer radiation-induced side effects than are conventional radiotherapy methods when combined with chemother-apy, according to preliminary data from two prospective studies conduct- ed at the University of Texas M.D. An-derson Cancer Center in Houston.

Significantly less esophagitis, pneumoni-tis, and bone marrow toxicity were observed with proton beam therapy (PBT) than with intensity-modulated ra-diotherapy (IMRT), Dr. Ritsuko Komaki reported at the European Society for Therapeutic Radiation Oncology An-iversary Conference.

Proton beam therapy also significant-ly reduced the incidence of esophagitis when compared with IMRT and three-dimen-sional conformal radiotherapy (3D-CRT). A mean esophageal dose of 40 Gy or higher was identified as the cut-off point for high-grade esophagitis occur-ring with any method.

Radiation dose escalation improves local control but increases toxicity, espe-cially when combined with concurrent chemotherapy for non–small cell lung cancer (NSCLC) or even small cell lung cancer,” said Dr. Komaki, a professor of radiation oncology at M.D. Anderson, which opened its 94,000-square-foot Pro-ton Therapy Center in 2006. As such, “ra-diation chemotherapy is a double-edged sword. It will kill cancer cells, but it also kills normal tissues, and more targeted treatment is needed,” she said.

“One of the most important benefits of PBT is that there is no exit dose,” Dr. Komaki said in an interview. “The protons stop after penetrating the tumor, and there is no dose of radiation beyond it.”

This has the potential to spare sur-rounding cells and organs from damage, she observed. Normal tissues that might be affected by radiation therapy for NSCLC include the lungs, esophagus, heart, and bone marrow, which cannot always be avoided by the use of 3D-CRT or even IMRT.

An expensive new technology that de-livers highly targeted radiation with elec-trically charged particles, PBT is promising but unproven, according to a 2009 review commissioned by the Agency for Healthcare Research and Quality. The authors found few com- parative studies to establish effectiveness or safety for the technology, which is housed in a small but growing number of proton beam centers that can cost $100 million to $225 million to build (Ann. Intern. Med. 2009;151:556-65).

Dr. Komaki and her associates are re-cruiting patients into the first prospective randomized trial to directly compare proton beam therapy with IMRT in in-ascendable stage II and III NSCLC. The phase II trial is supported by a grant from the National Cancer Institute, and involves treatment with 74-Gy PBT or IMRT with concurrent carboplatin and paclitaxel. To date, 107 of the planned 168 patients have been enrolled in the study at the Texas institution and at Mas-sachusetts General Hospital in Boston, the other participating center, she said.

A recent report from M.D. Anderson showed that higher doses of proton ra-diation could be delivered to lung tumors with a lower risk of esophagitis and pneumonitis than either IMRT or 3D-CRT (Cancer 2011;117:3004-13).

The new data presented by Dr. Ko-maki showed significantly reduced rates of grade 2 or higher esophagitis (P less than .001), pneumonitis (P less than .002), hematologic toxicities (P less than .001 for neutrophil toxicity and P less than .001 for hemoglo-bin and white blood cell toxicities), and fatigue (P less than .001) than with IMRT.

Data Source: Two retrospective studies: one involving 135 patients with NSCLC treated with concurrent chemoradiation (PBT, IMRT) and one involving 678 pa-tients with NSCLC treated with concurrent chemoradiation between 1999 and 2008.

Disclosures: Dr. Komaki and Dr. Gomez, stated they had no financial conflicts of interest.

Major Finding: PBT resulted in significant-ly lower rates of grade 2 or higher esophagitis (P less than .001), pneumo-nitits (P less than .002), hematologic toxicities (P less than .001 for neutrophil toxicity and P less than .001 for hemoglo-bin and white blood cell toxicities), and fatigue (P less than .001) than with IMRT.

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Calculations showed a hazard ratio for overall survival of 0.36 for the patients who did not get crizotinib compared with those who did (P = .004).

‘These results suggest that crizotinib may significantly im-prove survival outcomes in pa-tients with advanced ALK-positive NSCLC,” Dr. Shaw said.

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Gene Test Helps Assess Stage I and II Lung Cancer

BY MITCHEL L. ZOLER
Elsevier Global Medical News

AMSTERDAM – A commercially available genetic test significantly improved discrimination between low- and high-risk stage I and IIa lung cancer patients in a pair of validation tests, leading investigators to propose routine use of the test to identify early-stage patients who should get adjuvant chemotherapy.

“The multigene assay can outperform conventional risk factors and staging, and may lead to personalized therapies for patients with early-stage nonsquamous non–small cell lung cancer,” Dr. Johannes Kratz said at the World Conference on Lung Cancer.

Dr. Kratz conceded that no prospective, randomized study has yet tested whether identification of high-risk stage I patients singled out a subgroup that would definitely benefit from adjuvant chemotherapy. But the prognostic information that the genetic test already provides justifies its routine use in stage I and II patients, said Dr. Kratz, a surgeon who performed this study while at the University of California, San Francisco (UCSF), but is now at Massachusetts General Hospital in Boston.

“I think [the test] is certainly ready for prognosis, to give patients information,” he said in an interview. “We’ll start using it routinely for prognosis at UCSF. We believe the strength of the results shows it’s ready for prime time. Whether it should also be used to guide treatment, especially for stage I patients, is up to each health care provider, but it opens an interesting possibility before anything is proven in a randomized, controlled trial. The hope is that by identifying high-risk patients, you’ll improve their survival by giving them the right type of chemotherapy. And in some of the low-risk stage II patients, you can avoid some of the toxicities of adjuvant chemotherapy.”

Although several different genetic tests for stage I lung cancer have been studied over the past decade, none have wound up as marketed tests. Dr. Kratz and his associates set out to develop a practical and commercially viable test that would work in collaboration with Pinpoint Genomics, the company that has now begun marketing the test. The test they developed uses polymerase chain reaction-based gene expression assays for 11 different genes, based on results from prior studies that identified genes critical to key causal pathways leading to lung cancer. “We took a blindly drawn, one-shot approach,” in putting together the genetic test panel, without any tinkering during the validation phase to boost the prognostic strength of the test, he explained at the conference. It was developed by the International Association for the Study of Lung Cancer. They also focused on tests that use paraffin-embedded specimens.

Major Finding: Adding a commercially available genetic test to standard TNM staging significantly refined the prognosis of stage I and IIa patients. Patients identified as being at high risk for mortality by the genetic test had a statistically significant, 90% increased risk (P < .001) in a multivariate analysis in one validation cohort, and a threefold increased mortality risk (P < .001) in the second validation cohort.

Data Source: Validation cohorts of 433 nonsquamous non–small cell lung cancer patients collected by Kaiser Permanente of Northern California and 1,006 similar lung cancer patients collected by the Chinese Clinical Trials Consortium, and a training cohort of 361 similar lung cancer patients collected at UCSF.

Disclosures: Dr. Kratz said that he has been a consultant to and has an equity interest in Pinpoint Genomics, the company that developed the genetic test used in the study.

“I don’t think a prospective validation study is needed” before routine prognostic use of the test begins, he said. The validation studies were done retrospectively, but in a very controlled way that was equivalent to prospective validation. I think we have powerful evidence that these markers provide additional prognostic information. We’re not saying to abandon traditional staging, but this adds useful prognostic information.”

The initial test development cohort consisted of 361 stage I, II, and IIa patients treated by physicians from Kaiser Permanente of Northern California, and a second cohort of 1,006 patients with stage I, II, or IIa disease treated at hospitals affiliated with the Chinese Clinical Trials Consortium. Median follow-up in the three cohorts ranged from just over 3 years to just under 11 years; the second cohort was about 4.5 years.

The test was based on principles of lung cancer, and there was no information about the genetic test leading to a near doubling of the mortality risk in the Kaiser cohort (hazard ratio = 1.91, P < .001) and a more than tripling of the mortality risk in the Chinese cohort, compared with the low-risk tertile (HR = 3.25, P < .001).

Based on their findings, Dr. Kratz and his associates proposed a new variation on the conventional tumor size, lymph node status, metastases (TNM) staging system that they called TNMM; the second M stands for multigene assay.

The researchers also found that adding the gene test led to statistically significant increases in the area under the curve for prognostic accuracy.

BY SHARON WORCESTER
Elsevier Global Medical News

ORLANDO – Endobronchial dysplasia appears useful as a biomarker for improving the success of lung cancer chemoprevention, investigators reported at the annual meeting of the American Association for Cancer Research.

Bronchoscopies, along with biopsies of standard endobronchial sites and any other abnormal-appearing areas, were performed at baseline and at 6 months after enrollment. The patients are also are monitored at 12-month intervals for treatment with iloprost or placebo in a phase II chemoprevention trial involving 152 former or current smokers with at least a 20 pack-year history.

Former smokers who received iloprost, an oral prostacyclin analog approved for treatment of primary pulmonary hypertension, had significant improvements on several measures of endobronchial dysplasia, while current smokers had no improvement, Dr. Paul Bunn reported.

“The findings show that iloprost, which has been shown to prevent the development of lung cancer in various murine models involving cigarette-smoke exposure, also might have the same benefit for humans and thus deserves further study,” Dr. Bunn and his coauthors concluded.

The results also show that endobronchial dysplasia could serve as a biomarker for effectiveness of chemoprevention treatment — much as cholesterol does in patients being treated with statins to prevent cardiovascular disease, according to Dr. Bunn, executive director of the International Association for the Study of Lung Cancer and professor of lung cancer research at the University of Colorado, Aurora.

In the current study, baseline histology was significantly worse in current smokers than in former smokers (average biopsy scores of 3.0 vs. 2.1, respectively, with a score of 4 indicating mild dysplasia). Former smokers experienced a 0.41-point improvement in average biopsy score (P = .010), but no improvement in their worst baseline biopsy score (P = .002), and a 12.5% improvement in dysplasia index (P = .006), which was the percentage of biopsies with a score of at least 4, said Dr. Bunn.

“The histologic improvement in the treated patients who were former smokers was larger than the magnitude of the difference between current and former smokers,” he said.

For example, the baseline dysplasia index in current and former smokers was 46% and 31%, respectively, but the pre- and post-treatment dysplasia index in former smokers was 43% and 19.6%, respectively.

Study participants had an average 30-pack-year history of smoking, and at least mild cytologic atypia on sputum cytologic examination. Patients also had no history of previous lung cancer. The treatment and placebo groups were well-matched for age, tobacco exposure and baseline histology, and there was no difference in dropout rate or serious adverse events between the treatment and placebo groups, Dr. Bunn noted.

People who quit smoking remained at a greater risk of lung cancer than are never smokers, and it is important to find effective chemopreventive measures for these individuals, he said.

Dr. Bunn discussed an off-label use of iloprost; he had no other disclosures.
Nitric Oxide Not Useful for Congenital Diaphragmatic Hernia

BY DOUG BRUNK
Elsevier Global Medical News

PALM DESERT, CALIF. – Nitric oxide use in neonates with diaphragmatic hernia remains widespread even though its efficacy remains to be proven, results from a large national analysis demonstrated.

Nitric oxide has been studied extensively in newborns with hypoxic respiratory failure,” Dr. Brendan T. Campbell said at the annual meeting of the American Pediatric Surgical Association. “There have been 14 randomized, controlled trials done in term newborns with respiratory failure, and two of those studies enrolled sufficient numbers of patients with congenital diaphragmatic hernia. Both studies demonstrated conclusively that treatment with nitric oxide does not improve outcomes in newborns with congenital diaphragmatic hernia.

The first of these studies, he said, found that patients treated with nitric oxide were actually 30% more likely to require extracorporeal membrane oxygenation than those who did not receive nitric oxide (Pediatrics 1997;99:538-45).

In an effort to describe national trends, inter-hospital variability in use, and costs associated with nitric oxide use in neonates with congenital diaphragmatic hernia (CDH), a health services research team led by Dr. Campbell analyzed records in the Pediatric Health Information System (PHIS) database. For the years 2003-2010, they identified all patients with a diagnostic code of CDH and a procedural code for CDH repair at 40 children’s hospitals that contribute data to the PHIS. Patients with congenital cardiac anomalies and inaccurate nitric oxide discharge data were excluded from analysis, said Dr. Campbell, a pediatric surgeon at Connecticut Children’s Medical Center, Hartford, and an assistant professor of surgery and pediatrics at the University of Connecticut.

The analysis identified a total of 3,651 infants with CDH; 514 infants with cardiac anomalies and missing or inaccurate data were excluded. The overall mortality rate was 15%, but the mortality rate for the 761 patients treated with nitric oxide was 47%, compared with roughly 5% for the 2,376 patients who were not treated with nitric oxide.

Patients treated with nitric oxide had a significantly longer median length of stay, compared with their counterparts (median of 31 days vs. 20 days; P < 0.001), and significantly higher median total charges (a median of $456,473 vs. $36,270).

Dr. Campbell estimated that the 761 patients treated with nitric oxide generated nearly $34 million in unnecessary hospital charges. “Reducing nitric oxide use in these patients would significantly lower costs without adversely affecting outcomes,” he said.

Wide variation in the use of nitric oxide in newborns with CDH existed among the 40 PHIS hospitals. At one hospital, for example, more than 50% were treated with nitric oxide, while the rate was 10% or less at two other PHIS hospitals.

Limitations of the study included its retrospective design and the potential for coding errors and missing data. Dr. Campbell said that he had no relevant financial conflicts to disclose.

The meeting was supported by a grant from Elsevier, which owns this news organization.

Nitric Oxide: A Strong or Weak Therapy?

Proposed explanations include pneumococcal serotype replacement and/or evolving antimicrobial resistance patterns, said Dr. Cohen of the Hospital for Sick Children, Toronto. He recently reported on 82 children with empyema – as defined by ultrasound evidence of pleural effusions with loculations – at the annual meeting of the Pediatric Academic Societies. The children were seen at 1 and 6 months post discharge, when they underwent clinical examination, a chest x-ray, quality-of-life assessment using the Peds-QL, and spirometry if they were at least 5 years old.

The median age of the subjects was 1.6 years; 27% of them had an organism isolated, most commonly Streptococcus pneumoniae. Of note, methicillin-resistant Staphylococcus aureus was not the causative organism in only one child. A chest drain was used in 51 children, and 40 of those also received fibrinolytics. The remaining patients were treated only with antibiotics.

Surgical assistance thoracic surgery was not employed. The average hospital stay was 10.8 days. Eight children went to the pediatric ICU at discharge, 21% of patients still had fever, which lasted up to 1 further week; 7% of children were re-admitted within 1 month.

At the 1-month follow-up, 18% of the patients had fever, 23% cough, and 2% failure to thrive; 95% of the school-age children had missed a median of 5 classroom days. By 6 months, however, only 16% of children were still coughing, and 30% of school-age children had missed an average of 2 days of school since the 1-month evaluation. None were ever extubated and failure to thrive at late follow-up.

At 1 month post discharge, 7 of 20 children had abnormal spirometry, defined as an FEV1 that was 80% or less of predicted. Of the 82 children, 24 had persistent abnormalities on chest x-ray, mostly effusion, pneumatocele, or abscess. Twelve of 68 parents rated their child’s health-related quality of life as abnormal based on the Peds-QL score more than 1 standard deviation below the normal population.

By 6 months, only one child had abnormal spirometry and three had persistent chest x-ray abnormalities. At 1 year, these abnormalities had resolved in three patients, while the fourth was lost to follow-up. Moreover, at 6 months, parents rated their child’s quality of life on the Peds-QL as similar to that in 8,410 healthy historical controls and significantly better than were the scores for 157 children with asthma, Dr. Cohen said.

He declared having no financial conflicts of interest.

No Negative Eye Effects Found With Long-Term ICS

BY DOUG BRUNK
Elsevier Global Medical News

SAN FRANCISCO – Using inhaled budesonide daily for chronic asthma for a mean of 16 years from childhood into adulthood didn’t cause more cataracts or significantly change intraocular pressure or vision in a prospective, longitudinal, placebo-controlled study.

Among 300 Danish patients taking inhaled budesonide for chronic asthma, 148 underwent eye examinations 15-20 years after the start of the study, and 53 of 163 healthy siblings in the control group. The exams detected two posterior subcapsular cataracts that were outside the central 3-mm zone, but both were in the control group and none in the budesonide group, Dr. Søren Pedersen and his associates reported at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

Nineteen cataracts in the budesonide group would have needed to be demonstrated to statistically significant 5% increased risk for cataracts, a poststudy power analysis found.

Average vision measurements were identical between groups (1.04 in each eye), said Dr. Pedersen of the University of Southern Denmark, Kolding. Intraocular pressures did not differ significantly between groups, with average measurements of 13.8 mm Hg in each eye of the asthma patients, and averages of 14.5 mm Hg in the right eyes and 14.2 mm Hg in the left eyes of the control group.

“This is a very strong finding’ of safety with long-term inhaled budesonide,” Dr. Pedersen said in an interview.

Patients took a mean daily dose of 385 mcg of budesonide and accumulated a mean dose of 2.3 g. Increased intraocular pressures (higher than 21 mm Hg) were seen in five patients (3.4%) and in one sibling in the control group (1.9%), a non-significant difference between groups. The accumulated dose of budesonide was not significantly associated with intraocular pressure, Dr. Pedersen said.

The study is part of a larger study that began with 270 children, including 62 with asthma who did not use inhaled corticosteroids, all of whom were evaluated for cataracts, bruises, growth, bone mineral density, and clinical effects of inhaled budesonide 4-6 years after treatment started, with no adverse effects found. At that point, 32 children in the control group dropped out, the other 30 shifted to the budesonide group, and 163 healthy siblings became the new control group. Patients were evaluated every 1-2 years.

The mean age of those who had eye exams 15-20 years into the study was 26 years for patients and 28 years for siblings. A total of 68% of patients and 47% of controls were male. Treatment duration ranged from 3 to 22 years. Daily budesonide dose ranged from 50 to 1,220 mcg. The accumulated budesonide dose ranged from less than 1 g to 8.8 g.

Previous studies of the risk of posterior subcapsular cataracts from oral or inhaled steroids were cross-sectional studies with little or no information on the dose of inhaled corticosteroid used, he said.

This is a very strong finding’ of safety with long-term inhaled budesonide.

Dr. Pedersen

Nitric Oxide: A Strong or Weak Therapy?

Dr. Burt Lesnick, FCCP, comments: The overwhelming evidence from clinical trials suggests that we should not be using inhaled nitric oxide for infants who have congenital diaphragmatic hernia. Strategies need to be implemented to enhance clinicians’ ability to adopt this change in practice.

Dr. Burt Lesnick, FCCP
Important safety information

Because of the risks of liver injury and birth defects, Tracleer may be prescribed and dispensed only through the Tracleer Access Program (T.A.P.), a restricted distribution program, by calling 1-866-228-3546. Only prescribers and pharmacies registered with T.A.P. may prescribe and distribute Tracleer. Tracleer may be dispensed only to patients who are enrolled in and meet all conditions of T.A.P.

Liver injury
Elevations of liver aminotransferases (ALT, AST) and liver failure have been reported with Tracleer. In a setting of close monitoring, rare cases of liver failure and unexplained hepatic cirrhosis were observed after prolonged treatment. In general, avoid using Tracleer in patients with elevated aminotransferases (>3 × ULN). Measure liver aminotransferases prior to initiation of treatment and then monthly. Discontinue Tracleer if aminotransferase elevations are accompanied by signs or symptoms of liver dysfunction or injury or increases in bilirubin ≥2 × ULN.

Teratogenicity
Based on animal data, Tracleer is likely to cause major birth defects if used during pregnancy. Exclude pregnancy before and during treatment. To prevent pregnancy, females of childbearing potential must use 2 reliable forms of contraception during treatment and for 1 month after stopping Tracleer unless the patient has a tubal sterilization or Copper T 380A IUD or LNG-20 IUS inserted, in which case no other contraception is needed. Monthly pregnancy tests should be obtained.

Contraindications
Tracleer is contraindicated with cyclosporine A, glyburide, in females who are or may become pregnant, or in patients who are hypersensitive to bosentan or any component of Tracleer.

Warnings and precautions
In clinical trials, Tracleer caused ALT/AST elevations (>3 × ULN) in 11% of patients accompanied by elevated bilirubin in a few cases. The combination of hepatocellular injury (increases in aminotransferases of >3 × ULN) and increases in total bilirubin (≥3 × ULN) is a marker for potential serious liver injury. Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. Avoid using Tracleer in patients with moderate or severe liver impairment or elevated ALT/AST >3 × ULN.

If clinically significant fluid retention develops, with or without associated weight gain, the cause, such as Tracleer or underlying heart failure, must be determined. Patients may require treatment or Tracleer therapy may need to be discontinued.

Preclinical data and an open-label safety study (N=25) showed a decline in sperm count of ≥50% in 25% of Tracleer-treated patients after 3 or 6 months. After 6 months, sperm count remained in normal range, with no changes in sperm morphology or motility, or hormone levels. Endothelin receptor antagonists such as Tracleer may adversely affect spermatogenesis.

Treatment with Tracleer can cause a dose-related decrease in hemoglobin (Hgb) and hematocrit. Hgb should be checked after 1 and 3 months, and then every 3 months. Upon marked decrease in Hgb, determine the cause and need for specific treatment.

If signs of pulmonary edema occur, the possibility of associated pulmonary veno-occlusive disease should be considered. Tracleer should be discontinued.

Adverse events
In Tracleer pivotal trials, the most common adverse events occurring more often in Tracleer-treated patients than in patients taking placebo (≥2%) were respiratory tract infection, edema, hypotension, sinusitis, arthralgia, liver function test abnormal, palpitations, and anemia.
CELEBRATING 10 YEARS OF PUTTING PATIENTS FIRST

Introducing the Tracleer Patient Coupon Program—patients pay no more than $10 per month for Tracleer.

Indication
Tracleer is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital systemic-to-pulmonary shunts (18%). Patients with WHO class II symptoms showed reduction in the rate of clinical deterioration and a trend for improvement in walk distance. Physicians should consider whether these benefits are sufficient to offset the risk of liver injury in WHO class II patients, which may preclude future use as their disease progresses.

Please see accompanying brief summary of prescribing information, including BOXED WARNING about liver injury and pregnancy, on following pages.

*Patients ineligible for the Tracleer Patient Coupon Program include any patients whose prescriptions are paid for by the government, Medicare, Medicaid, VA/DOD (Tricare), or Indian Health Service, patients in Massachusetts and Puerto Rico, or where prohibited by law.
WARNING: RISKS OF LIVER INJURY and TERATOGENICITY

Because of the risk of liver injury and birth defects, Tracleer® is contraindicated in pregnant patients and the use of Tracleer in breastfeeding women is not recommended. Use of Tracleer in females of child-bearing potential must use two reliable methods of contraception unless the patient has a tubal sterilization. throughout treatment and for one month after stopping use of Tracleer. If Tracleer is re-introduced it should be at the starting dose; aminotransferase levels should be checked within 3 days and if normal, treatment may be recommenced. If Tracleer causes at least 3-fold upper limit of normal (ULN) elevation of liver aminotransferases (ALT and AST) or increases in total bilirubin (≥ 3 x ULN) is a marker for potential serious liver injury. Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated.

Discontinuation

In patients with pro-existing hepatic impairment

Tracleer® 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 NYHA Functional Class II (125 mg twice daily) or WHO Class III (62.5 mg twice daily) PAH associated with connective tissue disease (CTD), and PAH associated with congenital systemic-to-pulmonary shunts (1%)

Dosage and Administration

Recommended Dosing

Table 1: Dosing Adjustment and Monitoring in Patients Developing Aminotransferase Elevations

Dosage and Adaptation

Elevations in aminotransferases require close observation (see Dosage and Administration, Warnings and Precautions). In these trials ranged from 1 day to 4.1 years (N=94 patients). Three hundred and twenty-two patients received bosentan ≥ 4 times the currently recommended clinical dose (125 mg twice daily). Fluid retention in patients with pulmonary hypertension occurring with bosentan monotherapy is associated with an increased risk of hospitalization for decompensating heart failure.

Dosage modifications of bosentan are usually necessary when bosentan is administered concomitantly with cytotoxic agents. However, a small increase in the risk of liver injury has been reported in patients who were treated with bosentan while receiving glyburide concomitantly with bosentan. Therefore, glyburide should not be initiated or continued concomitantly with bosentan.

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Dosage and Administration
Adverse Event | Bosentan | Placebo | N=256 | N=122
--- | --- | --- | --- | ---
No. | % | No. | %

Respiratory Tract Infection | 56 | 22% | 20 | 17%
Headache | 30 | 12% | 15 | 12%
Edema | 28 | 11% | 16 | 6%
Gastrointestinal | 13 | 5% | 8 | 5%
Flushing | 9 | 4% | 4 | 4%
Hypertension | 10 | 4% | 3 | 2%
Sinusitis | 9 | 4% | 4 | 4%
Arthralgia | 9 | 4% | 4 | 4%
Liver Function Test Abnormal | 7 | 3% | 4 | 3%
Fatigue | 6 | 3% | 3 | 3%
Anemia | 8 | 3% | 4 | 4%

*Note: only AEs with onset from start of treatment to 1 calendar day after end of treatment are included. All reported adverse events (at least 3%) are included except those too general to be informative, and those not reasonably associated with the use of the drug because they were associated with the condition being treated or were very common in the treated population.

Dosage and Administration

Bosentan is available as tablets containing 62.5 mg or 125 mg bosentan for oral administration. Each tablet contains 62.5 mg or 125 mg of bosentan base with the following inactive ingredients: lactose, microcrystalline cellulose, sodium starch glycolate, and titanium dioxide. The tablets are pink and white.

Bosentan Tablets 62.5 mg: Each tablet contains: bosentan 62.5 mg (active ingredient) and the following inactive ingredients: lactose, microcrystalline cellulose, sodium starch glycolate, and titanium dioxide. The tablets are pink.

Bosentan Tablets 125 mg: Each tablet contains: bosentan 125 mg (active ingredient) and the following inactive ingredients: lactose, microcrystalline cellulose, sodium starch glycolate, and titanium dioxide. The tablets are white.

Bosentan Tablets 250 mg: Each tablet contains: bosentan 250 mg (active ingredient) and the following inactive ingredients: lactose and microcrystalline cellulose. The tablets are white.

Bosentan Tablets 375 mg: Each tablet contains: bosentan 375 mg (active ingredient) and the following inactive ingredients: lactose, microcrystalline cellulose, and titanium dioxide. The tablets are white.

Bosentan Tablets 500 mg: Each tablet contains: bosentan 500 mg (active ingredient) and the following inactive ingredients: lactose and microcrystalline cellulose. The tablets are white.

The changes in plasma concentrations were not considered clinically relevant and dose adjustments are not necessary. This recommendation holds true when alimeninol is used for the treatment of pulmonary arterial hypertension or esophageal dysfuction.

Informed consent. In some volunteer, co-administration of multiple doses of 125 mg twice daily bosentan and 80mg three times daily sildenafil resulted in a reduction of sildenafil plasma concentrations by 67% and increased bosentan plasma concentrations by 56%. The changes in clinical parameters were not considered clinically relevant and dose adjustments are not necessary. This recommendation holds true when sildenafil is used for the treatment of pulmonary arterial hypertension or esophageal dysfuction.

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Sleep Apnea Tied to Diabetic Retinopathy, Neuropathy

BY SHERRY BOSCHERT
Elsevier Global Medical News

SAN DIEGO – Obstructive sleep apnea in patients with type 2 diabetes predicted a three- to fourfold higher risk for diabetic peripheral neuropathy or sight-threatening retinopathy, separate analyses found.

The results suggest that OSA may play a role in the development of peripheral neuropathy and sight-threatening retinopathy in people with diabetes, Dr. Abd Tahrani and his associates reported at the meeting the annual scientific sessions of the American Diabetes Association. Ongoing studies are exploring the possible mechanisms involved.

Further research also is warranted on the possibility that treating OSA might affect the development or progression of retinopathy or neuropathy, added Dr. Tahrani of the University of Birmingham (England), where he is a research fellow for the U.K. National Institute for Health Research.

The prospective studies recruited random patients from a hospital-based, outpatient diabetes clinic in the United Kingdom. Individuals were excluded if they had a known respiratory disorder, including OSA. Patients had a mean age of 59 years and a mean 11-year history of diabetes, and 46% were white.

Participants underwent one night of home-based multichannel respiratory monitoring, and were considered to have OSA if they had an apnea-hypopnea index of at least 5 events per hour. In 224 patients who also were assessed for sight-threatening retinopathy, 63% had OSA and 38% had sight-threatening retinopathy. Patients with OSA were significantly more likely to have sight-threatening retinopathy (48%) than were patients without OSA (20%).

The study defined sight-threatening retinopathy as the presence of preproliferative or proliferative retinopathy, maculopathy, or the need for laser treatment.

After adjustment for a wide range of potential confounders, patients with OSA were 3.6 times more likely to have sight-threatening retinopathy, 5 times more likely to have advanced diabetic retinopathy, and 4.4 times more likely to have maculopathy than were patients without obstructive sleep apnea.

In a separate study by the same investigators involving 231 patients who were assessed for both OSA and peripheral neuropathy, 65% had OSA and 45% had diabetic peripheral neuropathy. Patients with OSA reported more neuropathic symptoms.

Among patients with OSA, 60% had diabetic peripheral neuropathy, compared with 27% of patients without sleep apnea. OSA conferred a significant threefold higher risk for peripheral neuropathy after adjustment for a wide variety of potentially confounding variables, Dr. Tahrani reported. The severity of peripheral neuropathy correlated with the severity of sleep apnea.

OSA was prevalent in 75% and 52% of white and South Asian patients, respectively. Likewise, diabetic peripheral neuropathy was more prevalent in whites (56% vs. 40%). Both differences were significant.

The lower prevalence of OSA in the South Asian patients might be one reason for the lower prevalence of diabetic peripheral neuropathy, the investigators suggested.

Dr. Tahrani reported having no conflicts of interest.

Sleep Deficit Costly

Toll • from page 1

preschool predict sleep duration at kindergarten," she explained.

Controlling for the outcome of interest at the preschool time point, sex, ethnicity, and family income, researchers found that less sleep at preschool significantly predicted worse scores on parent-reported hyperactivity and attention at kindergarten, whereas less sleep predicted hyperactivity and attention at preschool did not predict sleep duration at kindergarten, Dr. Gaylor stated. “These findings suggest that for children who are not getting adequate sleep may be at risk for developing behavioral problems manifested by hyperactivity, impulsivity, and problems sitting still and paying attention," she said. The results extend those of a previous study in which she and her colleagues determined that having a consistent bedtime was the most reliable predictor of positive developmental outcomes by age 4 years, she noted.

The Obesity Link

In a twin study designed to look more closely at the previously reported link between short sleep duration and elevated body mass index, Dr. Nathaniel Watson of the University of Washington in Seattle and his colleagues determined that short sleep may potentiate an underlying genetic mechanism.

The investigators examined whether sleep duration modified genetic and environmental influences on BMI in 1,811 pairs of twins drawn from the population-based University of Washington Twin Registry. The mean age of the study participants was 36.6 years. The participants provided self-reported information on height and weight, which was used to calculate BMI, as well as on habitual sleep duration, Dr. Watson said. The mean BMI of the group was 25.4 kg/m², and the mean sleep duration was 7.18 hours, he said.

Using behavioral genetic interaction models, the investigators found significant relationships between habitual sleep duration and genetic and shared environmental influences on BMI. Specifically, longer sleep duration was associated with decreased BMI, Dr. Watson reported. “When sleep duration was 7 hours or more, the predictiveness of BMI was more than double (70%) that observed when sleep duration was 9 hours (33%),” he said, noting that “there appears to be something about short sleep that creates a permissive environment for expression of obesity-related genes.” Similarly, he added, longer sleep duration may suppress genetic influences on body weight.

The findings are an important addition to the existing body of research on the relationship between sleep duration and BMI, Dr. Watson said. “Studies attempting to identify specific genotypes for BMI may benefit from considering the moderating role of sleep duration.”

A connection between sleep and lack of self-control with respect to dietary choices may also contribute to the sleep loss/obesity equation, according to a study presented by William Killgore, Ph.D., of Harvard Medical School in Boston.

To test their hypothesis that greater daytime sleepiness correlates with reduced prefrontal cortex response during passive viewing of images of high-calorie foods, Dr. Killgore and his colleagues analyzed the functional magnetic resonance imaging (fMRI) scans of 12 healthy adults obtained while they were shown pictures of high-calorie foods, low-calorie foods, and control images of plants and rocks. Using a second-level regression model, the researchers correlated the fMRI findings with subjects’ self-reported daytime sleepiness, assessed via the Epworth Sleepiness Scale (ESS).

“Greater ESS scores correlated with reduced activation in the dorsolateral prefrontal cortex when high-calorie vs. low-calorie food images were perceived,” Dr. Killgore reported, noting that this region is typically implicated in attention and inhibitory processing. Similarly, greater daytime sleepiness was also associated with increased activity in the right posterior inferior temporal cortex, he said.

The findings suggest the possibility that sleepiness may affect an individual’s inhibitory control while engaging in activities that predict their decision to highly appetizing, high-calorie foods, according to Dr. Killgore, although it’s uncertain as of yet whether the observed patterns relate to actual food consumption, he said.

Marital Discord

Although most sleep researchers focus on the individual, the fact that sleep problems and relationship trouble often co-occur led Wendy M. Troxel, Ph.D., of the University of Pittsburgh, and her colleagues to consider the dyadic nature of sleep in a recent study. The investigators examined the bidirectional links between nightly sleep and daily marital interactions among 35 healthy married couples (mean age, 32 years) by correlating the actigraph results for sleep latency, wakefulness after sleep onset, and total sleep time of each partner over 10 nights, with daily self-reported positive and negative marital interactions assessed via electronic diaries during the same period.

“We found stronger evidence linking sleep to the next day’s marital interactions, rather than the reverse direction,” reported Dr. Troxel. Specifically, wives’ positive and negative emotions consistently predicted their own and their husbands’ reports of more negative and less positive interactions the next day, even after adjusting for expressed emotions, whereas the quality of marital interactions did not appear to predict sleep measures in women, she said. The sleep quality of husbands did not appear to affect their own or their wives’ reports of next-day marital interactions; however, for men, a higher level of positive marital interactions was associated with a shorter total sleep duration the next night.

The findings suggest, perhaps, that “men are more likely to repress their feelings or not be as aware” of mood changes, whereas as women are more likely to express their emotional concerns and to “drive the emotional climate of the relationship,” Dr. Troxel said. “The results highlight the potential interpersonal consequences of sleep disorders, and as such may have important clinical implications, she said.

The presenters reported no financial conflicts relevant to their respective presentations.
Jaw Surgery Limits Severe Sleep Apnea in Soldiers

BY DIANA MAHONEY

MINNEAPOLIS – Maxillomandibular advancement may be a reasonable option for patients who have severe sleep apnea and are unable to tolerate continuous positive airway pressure therapy, according to a study by the Department of Veterans Affairs.

In maxillomandibular advancement (MMA), the upper and lower jaws are moved forward to optimize the airway and minimize soft-tissue blockages. Dr. Vincent Mysliwiec, FCCP, and his colleagues in the Critical Care Medicine and Sleep Medicine Service at Madigan Healthcare System, Joint Base Lewis-McChord, Tacoma, Wash., evaluated outcomes in an active-duty population.

“Obstructive sleep apnea is an increasingly common diagnosis in soldiers, and those soldiers with more severe cases are not deployable without going through an extensive waiver process,” Dr. Mysliwiec said at the annual meeting of the Associated Professional Sleep Societies. “We wanted to assess whether [MMA] represents a surgical cure that can potentially remove the requirement for CPAP in these individuals and, in so doing, increase the number of soldiers who are fully deployable.”

The researchers reviewed all of the MMA procedures performed for obstructive sleep apnea at their institution in 2006-2009 and identified 37 soldiers who had severe disease – defined as an apnea-hypopnea index (AHI) of more than 30 events/hr – and underwent the surgery as well as pre- and postoperative polysomnography. The primary study outcomes were comparisons of the pre- and postoperative AHI and minimum nocturnal oxyhemoglobin saturation. Surgical cure was defined as an AHI reduction of at least 50%, compared with preoperative AHI, and a postoperative AHI of less than 15.

The mean body mass index of the study cohort was 28 kg/m², and the mean preoperative AHI was 50.5. Dr. Mysliwiec reported. Following the procedure, “the mean postoperative [AHI] dropped significantly to 13.8,” he said. “Twenty-two of the soldiers – nearly 60% of the group – reduced their [AHI] by at least half, which met the criteria for surgical cure.”

Further, he said, 16 of the soldiers had a postoperative AHI of less than 5, “meaning they had no residual disease at all following the procedure.” One study patient did not experience a clinically significant reduction in AHI following the surgery. The mean minimum nocturnal oxyhemoglobin saturation increased postoperatively from 85% to 86%, a nonsignificant change (P = .21; standard deviation for both measures, 7%).

“Maxillomandibular advancement significantly reduced the severity of sleep apnea for our patients and improved the quality of their sleep,” Dr. Mysliwiec said. “These findings could improve the standard of care for civilians and active-duty service members with severe obstructive sleep apnea who can’t tolerate CPAP or have failed other soft-tissue procedures.”

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In just six minutes Shape® can help drill down to the root cause of exertional dyspnea – right in the clinic. Shape is simple, objective and intuitive. With our pay-per-procedure plan there’s no cost for the device. Shape elevates cardiopulmonary exercise testing to a new level.

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Make No Little Plans

How did we do?
For starters, the College ended the fiscal year in a strong financial position, with a $2.26 million positive bottom line. We surmounted the 18,000 membership mark; the CHEST Journal received the highest impact factor and ranking in its 75-year history; the largest number of international registrants attended CHEST 2010; and the CHEST Foundation launched its new branding campaign, Web site, and public-facing program, OneBreath™. Make The Most Of It.

Most recently, the American Board of Internal Medicine approved our performance improvement module on VTE prevention for MOC credit. We took our first train-the-trainer program for simulation education to Saudi Arabia. We launched the CHEST Journal podcast series. The Foundation also had the highest number of assets in the last 5 years—$9 million—closing FY 2011 with an $822,000 gain. In short, the ACCP met or exceeded the demanding metrics that we delineated in our strategic plan.

ACCP Strategic Plan 2011-2012
The ACCP Strategic Plan 2011-2012 builds on our strategic plan from last year in several key ways. First, an updated vision statement reflects our commitment to eliminating disparities in health care. Second, this streamlined plan focuses on a few critical goals for the ACCP as a whole; and, third, for the first time, the College articulates its core values—the foundation for how we achieve our mission and vision. 

The ACCP Strategic Plan 2011-2012 also includes ambitious and forward-looking strategies to achieve identified goals, along with metrics to rigorously track progress along the way. The Foundation plays a prominent role, as well, by, for example, increasing public awareness through its OneBreath™ campaign. Following are highlights from the ACCP Strategic Plan 2011-2012.

► Our Mission and Vision: Why the ACCP exists and what the College expects to be.

Mission: To promote the prevention, diagnosis, and treatment of chest diseases through education, communication, and research.

Vision: As the global leader in providing education in cardiopulmonary, critical care, and sleep medicine, the ACCP will promote diversity to optimize health, advance patient care, and support research while fostering health equity.

► Our Goals: How the ACCP will realize its vision.

Goal 1: Continue to implement a new association management system (AMS). Improving our technology infrastructure, including integrating and implementing a new AMS, is key to moving the College forward in all areas.

Goal 2: Maintain a strong and diverse financial base. Sound financial planning, along with identifying and securing alternative revenue sources, is integral to supporting ACCP efforts.

Goal 3: Maintain and diversify our successful programs (eg, AQuIRE, simulation, development of education products). Providing the best clinical education in chest medicine necessitates expanding and diversifying existing ACCP programs, such as AQuIRE, simulation, and the development of education products.

Goal 4: Grow ACCP membership in various ways, such as expanding categories for international, fellows-in-training, nonphysician providers, and others. Targeting key segments for membership growth, as well as implementing alternative membership models and policies, enhances the inclusiveness, efficiency, and financial position of the ACCP.

Goal 5: Increase public awareness/branding of the ACCP. The ACCP strengthens its impact by forging new partnerships with health-care and other societies, as well as by reaching out to the public through the OneBreath™ campaign.

Goal 6: Ensure that the ACCP leadership structure is strategically aligned to advance College priorities. Exceptional goals demand exceptional leadership. The College will continuously develop its current and future leaders to meet identified and organizational needs.

► Our Core Values: The foundation for how the ACCP achieves its mission and vision; the organizational culture that we aspire to and how we treat one another and our constituents.

Colligility: We foster collegiality between and among members and staff in all ACCP activities.

Innovation: We cultivate innovation through an atmosphere of creativity, optimism, and empowerment.

Transparency: We promote transparency by ensuring access to appropriate and accurate information for members, staff, other stakeholders, and interested members of the public.

Diversity: We promote diversity of background, experience, and other needed resources at all levels of the ACCP.

Excellence: We strive for the highest standards in everything that we do.

Integrity: We treat members, staff, and other stakeholders with integrity by accepting responsibility for our actions, being truthful, and following through with commitments.

Results-Oriented: We are results-oriented. We measure our progress toward the ACCP mission and vision, as well as evaluate the performance of our programs and services.

We thank our leaders and staff, who thoughtfully considered what it meant to take the ACCP to the next level and how to get there. Those deliberations from an environmental snapshot and March 2011 planning session formed the basis for the ACCP Strategic Plan 2011-2012. While we are proud of the work presented here, the current plan is by no means a finished product. Leaders and staff will implement identified strategies and ensure that programs and activities are aligned with the plan. The Board of Regents also will make certain that the College is on course to achieve its goals and modify the plan, as necessary.

Indeed, our strategic plan will become a way of life at the ACCP guiding decision making at all levels.

The ACCP creates its future through effective strategic planning. We are excited about this propitious future and trust that you will be, as well. We welcome your comments regarding your ACCP Strategic Plan 2011-2012 and look forward to rolling up our sleeves with you—as College leaders, members, and other supporters—to realize this “big plan.” As Burnham led the development of major cities like Chicago and Washington, DC, so too will the ACCP move forward as the global leader in clinical education for chest medicine.

From The CEO

Make No Little Plans

With Burnham’s words in mind, the Board of Regents approved the ACCP Strategic Plan 2011-2012 in June. However, the process that led to this blueprint for the future of the College originated last year. At that time, ACCP leaders and staff “thought big” by identifying and acknowledging our core competency—providing the best clinical education in chest medicine—and updated our mission and vision statements accordingly. We developed the first-of-its-kind ACCP strategic plan, which set ambitious goals that looked several years ahead and outlined specific strategies and metrics for measuring our success.

“Make no little plans. They have no magic to stir men’s blood and probably themselves will not be realized. Make big plans; aim high in hope and work, remembering that a noble, logical diagram once recorded will never die, remembering that a noble, logical diagram once recorded will never die, but long after we are gone will be a living thing, asserting itself with ever-growing insistence. ... Think big.” —Daniel Burnham, architect and urban planner, 1846-1912

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Integrative Oncology is a synthesis of mainstream treatment and complementary therapies in cancer care. Complementary therapies are noninvasive and nonpharmacologic adjuncts to mainstream cancer treatment. These therapies do not directly affect or treat disease but help to relieve pain and distress by controlling physical and emotional symptoms.

In the late 1990s, the Memorial Sloan-Kettering Cancer Center (MSKCC) Board of Overseers acted on its consensus that optimal patient care requires more than expert cancer management and mandated a broader emphasis on an integrative approach to better manage patients’ physical and emotional needs. The author was recruited to actualize this concept, and MSKCC has since developed an Integrative Medicine Service (IMS) within the Department of Medicine that can serve as a prototype for other centers around the world. The IMS provides clinical care, as well as research and training in collaboration with clinicians, researchers, and others throughout the institution. The service has also created a Web site to provide physicians and the public with “solid” information about herbal remedies, vitamins, and other dietary supplements (www.MSKCC.org/AboutHerbs).

A primary focus of the IMS is to study and deploy evidence-based, rational, complementary therapies to patients, their families, and staff. These approaches may be perceived as extensions of the supportive care previously associated with oncology for decades. Simultaneously, the IMS works diligently to curtail the use of “alternative,” unproven therapies promoted for use in lieu of mainstream cancer treatment, such as quackery.

The ICU staff requests integrative medicine consultations to reduce patient agitation, relieve pain, or reduce levels of narcotics needed to maintain comfort. These interventions are cost-effective and produce no negative side effects. Complementary therapies help normalize and humanize the high-tech ICU environment. Such consultations are also used by the ICU team to assist in navigating challenging interactions with patients and family members who insist on using “alternative” therapies (ie, magnet and light therapies, herbs, and supplements).

Integrative therapies available to IMS patients include massage therapy, mind-body techniques, music therapy, acupuncture, and herbal and supplements, as well as the provision of information about some herbal compounds and other dietary supplements. Each of these has a role in critical care.

**Massage Therapy**

The main goal of massage therapy in the ICU is to reduce physical pain, induce relaxation, and provide comfort. Touch therapies, such as foot massage, also offer the benefits of a caring interaction and the human touch. The type of massage intervention is determined by the patient’s clinical status and preference. In the hands of licensed massage therapists trained to work with cancer patients, this is a very safe and therapeutic intervention. MSKCC has offered massage therapy in the ICU for many years. A 3-year study conducted at MSKCC of 1,290 study patients showed that massage therapy brought sustained relief from pain, fatigue, nausea, and other symptoms. Specifically, scores were reduced by approximately 50%, even in patients who reported high baseline scores. Importantly, the benefits persisted for many patients throughout a 48-hour follow-up period (Cassileth et al. J Pain Symptom Manage. 2004; 28[3]:244).

**Mind-Body Techniques**

Mind-body interventions, including meditation, self-hypnosis, yoga, qigong, and tai chi use the mind’s capacity to influence bodily function and symptoms. Multiple studies demonstrate that meditation decreases pain, anxiety, stress, and insomnia in cancer patients. A 2007 study assessed the value of presurgical acupuncture for decreasing the need for intra-operative anesthesia and analgesics, as well as lowering the side effects associated with breast cancer surgery. Subjects in the hypnosis group required less propofol and lidocaine as compared with the control group. They also reported less pain intensity and unpleasantness (Montgomery et al. J Natl Cancer Inst. 2007; 99[17]: 1304). Both meditation and self-hypnosis, a deeper form of meditation, can easily be learned by patients and family members and applied, when needed, to relax and reduce stress. These stress reduction approaches are tools with which patients can help themselves, and a dose-response relationship exists, where better results are seen with more meditation practice.

**Music Therapy**

Music therapists, musicians with graduate training in music therapy, use music to reach patients. Music therapy is felt to encourage healing and promote well-being. Benefits from music therapy may be derived passively (patient listens) or interactively (patient participates). The music can be tailored to the patient’s preference in terms of the music selected and the instruments used. Typically, we bring portable instruments to the ICU, being weaned off sedatives and helps patients relax during procedures, such as extubation. In a serendipitous result of a music therapy study designed for patients, the attendant physicians and nurses unexpectedly experienced helpful emotional, cognitive, and team effects (O’Callaghan and Magill. Palliat Support Care. 2009;7[2]:219).

**Acupuncture**

Acupuncture is a 3,000-year-old component of traditional Chinese medicine. It involves stimulating one or more predetermined points on the body with sterile, filiform needles, which are approximately the width of human hair. The needles target specific acupuncture points on the body that are dense with sensory receptors. These acupoints have lower electrical resistance and are closer to superficial nerve junctions (Ma. J Altern Complement Med. 2003;9[2]:207).

Acupuncture reduces many symptoms experienced by cancer patients in all stages of treatment, including dyspnea, fatigue, hot flashes, sexual dysfunction, urinary problems, osteoarthritis, neuropathy, xerostomia, and more. Most relevant to patients in the ICU, acupuncture can relieve anxiety, depression, stress, and pain, and it can reduce the amount of opioids required to maintain patient comfort. Randomized clinical trials show that relief offered by acupuncture is not a placebo effect. A phase III MSKCC trial reported that acupuncture reduced pain and dysfunction in cancer patients with a history of neck dissection. In addition, acupuncture relieved xerostomia in this population (Pfister et al. J Clin Oncol. 2010;28[15]:2565).

**Herbs and Supplements**

Many cancer patients turn to herbs in the misperception that, because the products are “natural,” they are safe. Herbs and most other dietary supplements are not recommended for cancer patients undergoing treatment or for people receiving prescription medications. In fact, MSKCC recommends that no herbs, high-dose vitamins, or antioxidants be taken during cancer treatment. This prohibition stems from the fact that herbal remedies, which are biologically active, may interact negatively with mainstream oncologic treatments or induce toxicities. Moreover, most dietary supplements are not standardized, many are contaminated, and there are often major discrepancies between ingredients listed on the label and the supplement’s actual components.

Problems caused by herbs include:
- Garlic, gingko, ginseng, vitamin E: interfere with blood coagulation
- Ephedra: lowers blood sugar
- St. John’s Wort, valerian: may affect blood levels of chemotherapy
- Kava: can cause kidney failure

Herb-drug interactions represent an important problem. The MSKCC AboutHerbs Web site (www.mskcc.org/AboutHerbs) offers routinely updated and comprehensive, evidence-based data on more than 250 herbs, botanicals, antioxidants, vitamins, botanical therapies, and more, at no charge. Portals are available for patients and physicians. In conclusion, integrative oncology can benefit patients, family members, and staff in the ICU by relieving symptoms of physical pain and emotional distress and maximizing the serenity of critically ill patients throughout their ICU stay.
Neuromuscular Respiratory Medicine, Women's Lung Cancer, EGFR Mutational Analysis

Pediatric Chest Medicine

Embrace the Spirit of Aloha Suggestions

This October, pulmonary experts from around the world will gather in Honolulu to promote respiratory health for children. The itinerary includes a variety of modalities, each designed to engage learners and stimulate discussion. It will include simulation laboratories, clinical workshops, and pulmonary puzzlers, to name a few. Hawaii is an especially appropriate venue for this meeting, since aloha is more than just a greeting. It encompasses a spirit of living—a joyful sharing of life. Take this time, not only to learn, but to refresh your spirit with new ideas and an enthusiasm for our profession.

With the rapid advances in technology, we have begun to see more technology-dependent children joining pediatric practices. With these machines requiring specific training and expertise, both in a home and hospital setting, it is important that pediatricians be proficient in these processes. Therefore, this year, the Subcommittee on Pulmonary Care of Patients With Neuromuscular Disease will offer a postgraduate course on Neuromuscular Respiratory Medicine, including pediatric and adult patients. It will be hosted by experts in the respiratory care of children with neuromuscular disease and will highlight evidence- and consensus-based guidelines. Overall, the number of pediatric topics has increased this year and will include controversies in pediatric lung transplantation, asthma in unusual environments, respiratory complications of sickle cell disease, and more. Access www.accpmeeting.org for details.

Dr. Dean Edell, FCCP, Steering Committee Member

Women's Health

Current Epidemic of Lung Cancer in Women

Lung cancer is now the number one killer of women, claiming the lives of more women each year than breast cancer, colon cancer, and cervical cancer combined. This shifting paradigm in lung cancer follows the smoking trend and tobacco advertisements targeted to women. The death rate from lung cancer in US women rose 600% from 1930 to 1997 due to increases in smoking (A Report of the Surgeon General, 2001). The incidence of lung cancer among women continues to grow by 0.5% per year. Although smoking is the major cause of lung cancer, nonsmoking women are found to be at greater risk for developing lung cancer than non-smoking men.

Molecular and genetic marker studies identify lung cancer as a collection of genetically distinct diseases. The National Comprehensive Cancer Network (NCCN) guidelines, issued by the American Society of Clinical Oncology (ASCO) for clinical management of lung cancer, recommend treating patients with drugs that target molecular drivers of their specific tumors.

Therefore, molecular and mutation analysis of diagnostic tumor tissue, such as epidermal growth factor receptor (EGFR), is critically important in lung cancer management.

Women, in particular, appear to have more frequent mutations in the EGFR as compared with men. The NCCN guidelines include EGFR mutational analysis as a category 1 recommendation in the evaluation of non-small cell lung cancer. Multiple trials focused on patients with known EGFR activating mutations have demonstrated a better response and progression-free survival for patients receiving an EGFR-tyrosine kinase inhibitor (TKIs), such as erlotinib or gefitinib compared with chemotherapy as first-line therapy. These studies have been shown to identify erlotinib sensitivity in the 88% of patients with wild-type EGFR. In addition, a set of a novel, five-gene expression signatures appeared to predict disease control with erlotinib in refractory non-small cell lung cancer irrespective of EGFR mutation. Disease control at 8 weeks was seen in 83% of patients with one gene signature vs 0% in those without it, and 64% vs 10% in a similar analysis of patients with and without the second signature (Cancer Discovery, 2011;11[1]:OF42). Women survive longer than men, regardless of the stage at diagnosis or treatment, but the overall survival with this disease remains dismal. We have much work to do. The importance of performing molecular tests at this time, in particular EGFR mutation analysis, with more on the horizon (EML4-ALK), cannot be overemphasized.

Dr. Daya Upadhyay, Steering Committee Member

Occupational and Environmental Health

Analysis of Exhaled Breath Condensate in Occupational and Environmental Lung Diseases

A noninvasive method of exhaled breath testing is becoming increasingly important in health and disease; however, exhaled breath analysis has not yet been widely used in occupational lung diseases. Although, study of fractional exhaled nitric oxide in exhaled breath condensate has evolved from a research tool into a clinical measurement, useful for diagnosing and monitoring asthma, very little is known about its use in occupational asthma. Despite significant molecular and biological advancements, newer methods have not been frequently used in conjunction with noninvasive tests in occupational lung diseases.

Current new technologies, such as infrared, electrochemical, chemiluminescence, very sensitive modern mass spectrometry, gas chromatography, and gas chromatography mass spectrometry, can now identify thousands of unique substances in exhaled breath. These substances include elemental gases like nitric oxide and carbon monoxide and a multitude of volatile organic compounds. Furthermore, exhaled breath contains aerosolized droplets collected as exhaled breath condensate (EBC), which is composed of airway lining fluid mainly formed by water vapor and aerosol particles. EBC contains several biomolecules, including leukotrienes, 8-iso prostanes, prostaglandins, nitric oxide-derived products, a wide range of metabolic end products, proteins, and a variety of cytokines and chemokines. This test is also suitable for longitudinal studies that can be used to monitor the disease progression or a response to therapy. EBC is a noninvasive, inexpensive, and easy to repeat test that can provide rapid analysis of biomarker levels in the setting of occupational and environmental exposure.

Specific gene expression profiling has tremendously influenced our understanding of the pathogenesis of several diseases. EBC can be used to identify gene expression profiles of target inflammatory mediators in asthma, such as IL-4, IL-17, RANTES, macrophage inflammatory protein (MIP)-1alpha, MIP-1beta, IL-8, IFNgamma-inducible protein (IP)-10, TNF-alpha, TGF-beta, and eotaxin-1. Since occupational and environmental agents induce airway sensitization causing robust inflammatory responses, application of advanced investigative technologies could be useful in environmental and occupational lung diseases. We used polymerase chain reaction (PCR) array analysis in conjunction with noninvasive EBC tests to examine the effects of ozone on human airways. PCR array performs gene expression analysis with real-time PCR sensitivity and the multi-gene profiling capability of a microarray. Unlike conventional microarray, PCR array analysis is pathway-focused and profiles the expression of a panel of genes relevant to a pathway or disease state. In our analysis, the expressions of multiple cytokine and chemokine genes, including IL-12, IL-13, CCL-5, CCL-11, and IL-13RA, were found to be highly unregulated in EBC on exposure to high ozone levels in humans. These findings suggest that EBC can be used to study gene expression profiles induced by environmental and occupational lung diseases. Integration of newer molecular and biological technologies with noninvasive exhaled breath analysis can be used to advance investigational approaches in environmental and occupational lung diseases.

Dr. Daya Upadhyay, Steering Committee Member

CHEST Journal Continues to Rise

The just-released 2010 Journal Citation Reports® (Thomson Reuters, 2011) data show that CHEST now has an impact factor of 6.519, another increase over the previous year’s citation ranking. CHEST is the third-ranked journal out of 46 respiratory journals—unique among the top tier for its clinical focus—and is only 0.066 points behind the second-ranked journal. In addition to publishing innovative, high-impact research, CHEST is leading the charge: the CHEST journal app for Apple was downloaded over 22,000 times, and the iPad® version is in the top 100 of all medical apps in iTunes®. Recent reviews of the CHEST and ACCP-SEEK apps from the physicians at MedicalApps applauded both apps for their ease of use and functionality.
DAIRESP™ (roflumilast) tablets Rx Only

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

Initial

U.S. Approval: ... home some souvenirs. 

CONTRADICTIONS

The use of DAIRESP is contraindicated in the following conditions:

Moderate to severe liver impairment (Child-Pugh B, C) [see Clinical Pharmacology (12.3)] and Use in Specific Populations (8.6).

WARNINGs AND PRECAUTIONS

Treatment of Acute Bronchospasm

DAIRESP is not a bronchodilator and should not be used for the relief of acute bronchospasm.

Psychiatric Qualities of Sedation

Treatment with DAIRESP is associated with an increase in psychi- atric adverse reactions (see Clinical Pharmacology (12.3)) and if psychiatric adverse reactions occur, then the dose of DAIRESP should be decreased to a lower dosing level. DAIRESP treated patients reported psychiatric adverse events, such as anxiety, depression, and hostility. (see Adverse Reactions (6.1)) and if psychiatric adverse reactions occur, then the dose of DAIRESP should be decreased to a lower dosing level. DAIRESP treated patients reported psychiatric adverse events, such as anxiety, depression, and hostility. (see Adverse Reactions (6.1)).

Daliresp does not use roflumilast for the treatment of asthma.

TABLE 1: Adverse Reactions Reported by 2% of Patients Treated with DAIRESP 500 mcg Daily and Greater Than Placebo

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo (%)</th>
<th>DAIRESP 500 mcg Daily (%)</th>
<th>DAIRESP 250 mcg Daily (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia</td>
<td>0.6</td>
<td>0.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.6</td>
<td>1.9</td>
<td>1.5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.6</td>
<td>1.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.5</td>
<td>1.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Bowel disorders</td>
<td>0.5</td>
<td>1.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Appetite decreased</td>
<td>0.3</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Constipation</td>
<td>0.4</td>
<td>1.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Flatus</td>
<td>0.3</td>
<td>1.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Flatulence</td>
<td>0.3</td>
<td>1.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0.6</td>
<td>1.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Liver function tests</td>
<td>0.3</td>
<td>1.8</td>
<td>0.3</td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>0.6</td>
<td>1.9</td>
<td>0.6</td>
</tr>
<tr>
<td>Insomnia</td>
<td>0.3</td>
<td>1.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Nightmares</td>
<td>0.3</td>
<td>1.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Hair color change</td>
<td>0.3</td>
<td>1.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Exacerbations</td>
<td>0.5</td>
<td>1.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Increased thirst</td>
<td>0.3</td>
<td>1.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Hypopotassemia</td>
<td>0.3</td>
<td>1.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Weight gain</td>
<td>0.3</td>
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<td>0.3</td>
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<tr>
<td>Weight loss</td>
<td>0.3</td>
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<td>0.3</td>
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<tr>
<td>Mucous membrane stuff</td>
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<td>1.5</td>
<td>0.0</td>
</tr>
<tr>
<td>Palate pain</td>
<td>0.0</td>
<td>1.5</td>
<td>0.0</td>
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<tr>
<td>Laryngospasm</td>
<td>0.0</td>
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<td>0.0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>0.0</td>
<td>1.5</td>
<td>0.0</td>
</tr>
<tr>
<td>Intestine infection</td>
<td>0.0</td>
<td>1.5</td>
<td>0.0</td>
</tr>
<tr>
<td>Urinary tract irritation</td>
<td>0.0</td>
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<td>Diabetic patients</td>
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<td>Glucose diagnosis</td>
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<td>Hyperglycemia</td>
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<td>Hyperlipidemia</td>
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<td>Hypertriglyceridemia</td>
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<tr>
<td>Hypercholesterolemia</td>
<td>0.0</td>
<td>1.5</td>
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</tbody>
</table>

DAIRESP is not a bronchodilator and should not be used for the relief of acute bronchospasm.

Psychiatric adverse reactions occur in patients treated with DAIRESP. DAIRESP should not be used in patients with a history of depression or suicidal thoughts or behavior. Screening patients can help identify those at increased risk and may reduce the potential risk of psychiatric adverse reactions. (see Adverse Reactions (6.1)) and if psychiatric adverse reactions occur, then the dose of DAIRESP should be decreased to a lower dosing level. DAIRESP treated patients reported psychiatric adverse events, such as anxiety, depression, and hostility. (see Adverse Reactions (6.1)).

RESULTS OF CLINICAL TRIALS

In 8 controlled trials, 3136 and 2067 patients were treated with DALIRESP 500 mcg once daily in four 1-year placebo-controlled trials. (see Clinical Studies (14.1)).

Patients treated with DALIRESP 500 mcg daily reported psychiatric adverse reactions. In 8 controlled trials, 3136 and 2067 patients were treated with DALIRESP 500 mcg once daily in four 1-year placebo-controlled trials. (see Clinical Studies (14.1)).

In these trials, 804 patients treated with DALIRESP reported an adverse reaction compared with 469 patients treated with placebo. (see Clinical Studies (14.1)).

The proportion of patients who discontinued treatment due to psychiatric adverse reactions was 2.1% for DALIRESP-treated patients and 1.5% for placebo-treated patients. The most common adverse reactions that led to discontinuation of DALIRESP were diarrhea (1.0%) and flatulence (1.0%).

Serious adverse reactions, whether considered drug-related or not to the investigator, which were considered severe psychiatric adverse reactions to DALIRESP-treated patients included diarrhea, atrial fibrillation, lung cancer, suicide attempt, anxiety, and psychotic disorder. Table 1 summarizes the adverse reactions reported by 2% of patients in the DALIRESP-treated group in controlled clinical trials.

Nonpsychiatric effects: DALIRESP has been shown to adversely affect weight and food intake. When patients were treated with the drug during pregnancy and lactation periods in mice. In these studies, the effects of DALIRESP on food intake were observed to be approximately 48 times the MRHD on a mass basis at a maternal dose of 12 mg/kg/day during pregnancy and lactation. DALIRESP does not use roflumilast for the treatment of asthma.

Drug Interactions

A major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP3A4 and CYP1A2. The metabolism of roflumilast is not affected by concurrent systemic exposure to rifampicin (e.g., rifampicin, phenobarbital). The metabolism of roflumilast is not affected by concurrent systemic exposure to rifampicin (e.g., rifampicin, phenobarbital). The metabolism of roflumilast is not affected by concurrent systemic exposure to rifampicin (e.g., rifampicin, phenobarbital). The metabolism of roflumilast is not affected by concurrent systemic exposure to rifampicin (e.g., rifampicin, phenobarbital). The metabolism of roflumilast is not affected by concurrent systemic exposure to rifampicin (e.g., rifampicin, phenobarbital). The metabolism of roflumilast is not affected by concurrent systemic exposure to rifampicin (e.g., rifampicin, phenobarbital). The metabolism of roflumilast is not affected by concurrent systemic exposure to rifampicin (e.g., rifampicin, phenobarbital). The metabolism of roflumilast is not affected by concurrent systemic exposure to rifampicin (e.g., rifampicin, phenobarbital). The metabolism of roflumilast is not affected by concurrent systemic exposure to rifampicin (e.g., rifampicin, phenobarbital). The metabolism of roflumilast is not affected by concurrent systemic exposure to rifampicin (e.g., rifampicin, phenobarbital). The metabolism of roflumilast is not affected by concurrent systemic exposure to rifampicin (e.g., rifampicin, phenobarbital). The metabolism of roflumilast is not affected by concurrent systemic exposure to rifampicin (e.g., rifampicin, phenobarbital). The metabolism of roflumilast is not affected by concurrent systemic exposure to rifampicin (e.g., rifampicin, phenobarbital). The metabolism of roflumilast is not affected by concurrent systemic exposure to rifampicin (e.g., rifampicin, phenobarbital). The metabolism of roflumilast is not affected by concurrent systemic exposure to rifampicin (e.g., rifampicin, phenobarbital). The metabolism of roflumilast is not affected by concurrent systemic exposure to rifampicin (e.g., rifampicin, phenobarbital). The metabolism of roflumilast is not affected by concurrent systemic exposure to rifampicin (e.g., rifampicin, phenobarbital). The metabolism of roflumilast is not affected by concurrent systemic exposure to rifampicin (e.g., rifampicin, phenobarbital). The metabolism of roflumilast is not affected by concurrent systemic exposure to rifampicin (e.g., rifampicin, phenobarbital). The metabolism of roflumilast is not affected by concurrent systemic exposure to rifampicin (e.g., rifampicin, phenobarbital). The metabolism of roflumilast is not affected by concurrent systemic exposure to rifampicin (e.g., rifampicin, phenobarbital). The metabolism of roflumilast is not affected by concurrent systemic exposure to rifampicin (e.g., rifampicin, phenobarbical...
Top Practice Management Tips You Should Consider

1. Don’t be penalized—begin using an EMR.
2. Use the 6-min walk test, CPT code 92250, to measure oxygen desaturation.
3. Remember modifier 25 on E&Ms when procedures are performed the same day.
4. Develop and maintain an active practice compliance plan.
5. Maintain ongoing education and training of physicians and staff working on coding and reimbursement issues, and conduct regular in-services.
6. Encourage coding and billing staff to obtain credentials.
7. New ICD-9-CM codes for interstitial lung disease (adult and pediatric ILD diagnosis codes) and many other codes of interest to pulmonary, critical care, and sleep medicine will be effective on October 1, 2011.
8. Identify the correct Place of Service (POS) on each claim.
9. Be familiar with both national and local coverage decisions by Medicare and other insurers.
10. Know your Medicare Administrative Contractor (MAC) Medical Director, your Durable Medical Equipment (DME) MAC Medical Director, and your ACCP pulmonary CAC representative. Consider getting involved as a CAC representative or alternate.
11. Develop a policy to appeal inappropriately denied claims and partial payments and follow it.
12. Review frequency of CPT codes billed yearly per provider to look for change.

Questions? Contact Marla Brichta at mbrichta@chestnet.org.

FROM THE DESK OF THE PRACTICE MANAGEMENT COMMITTEE

ACCP Contractor Advisory Committee (CAC) Overview

By Dr. Robert Demarco, FCCP, Chair; and Donna Knapp Bybee, MA, FACMPE, Vice-Chair

The ACCP Practice Management Committee (PMC) invites your participation on the ACCP CAC.

In addition to the important work of Dr. Steve Peters, FCCP, as ACCP CPT Advisor; Dr. Mike Nelson, FCCP, as ACCP CPT Alternate Advisor; Dr. Scott Manaker, PhD, FCCP, RUC Internal Medicine Rotating Seat; Dr. Burt Lesnick, FCCP, RUC Internal Medicine Rotating Seat Alternate; Dr. Kathrin Nicolacakis, FCCP, as ACCP RUC Advisor; and their American Thoracic Society colleagues, Dr. Stephen Hoffmann, FCCP, for CPT; and Dr. Alan Plummer, FCCP, for RUC, there is the work of your state CAC representatives advocating for you on Medicare reimbursement issues.

The ACCP PMC is the group of physicians and practice managers/administrators working with Dr. Alan Barker, FCCP, the current Chair of the ACCP CAC. Dr. Barker plans to work with the ACCP Governors to fill the remaining openings for pulmonary CAC representatives. He reported that general trends affecting the Medicare population are routinely reviewed at every the CAC meeting. Recent, issues include recovery audit contractors, EHR implementation, PQRS, as well as policies put forward by Medicaid.

The ACCP CAC is a formal mechanism for ACCP pulmonary, critical care, and sleep medicine providers in each state to provide ACCP membership with a forum to discuss and improve administrative policies and exchange information between providers and contractors. ACCP CAC focuses on informing about and seeking collaboration on the development of local coverage determinations (LCDs). LCDs are documents that are produced by Medicare Administrative Contractors (MACs) that outline the acceptable medical necessity for Medicare Part A, Part B, and Medicare Advantage plans.

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ACCP Sleep Medicine Board Review 2011
August 26-29
San Antonio, Texas
Exam Date: November 10

ACCP Critical Care Medicine Board Review 2011
August 26-29
San Antonio, Texas
Exam Date: November 9

ACCP Pulmonary Medicine Board Review 2011
August 26-29
San Antonio, Texas
Exam Date: November 8

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medical necessity for a specific procedure. In order to support MACs with developing LCDs, each state is mandated to have a CAC made up of physicians from many different specialties. Pulmonary currently has a CAC representative in almost every state. The ACCP has organized these pulmonary CAC representatives into the ACCP CAC to promote collaboration.

ACCP CAC representatives:
- Provide a formal mechanism for ACCP pulmonary, critical care, and sleep medicine physicians in each state to be informed of, and participate in, the decisions (LCD) in an advisory capacity;
- Provide a mechanism to discuss and improve administrative policies that are within contractor discretion;
- Provide ACCP members a forum for information exchange;
- Improve relations between MAC medical directors and ACCP membership;
- Distribute proposed LCDs to colleagues in their respective state and to specialty societies in order to solicit comments;
- Update state colleagues and specialty societies on Medicare program changes announced at CAC meetings;
- Provide consensus recommendations approved by the ACCP PMC and the board when appropriate; and
- Discuss inconsistent or conflicting medical review policies.

The ACCP CAC has a quarterly conference call and also meets in person annually at CHEST. An agenda is being developed for the 2011 meeting in Hawaii. Dr. Arthur Lurvey, Palmetto GBA MAC Medicare Medical Director for American Samoa, California, Guam, Hawaii, Nevada, and Northern Marianas Islands, will be attending and providing presentations at:
- The CAC meeting, Sunday, October 23, 4:30 PM
- The Practice Operations NetWork (PON) meeting, Monday, October 24, 7:15 AM
- He will also be available following the PON meeting, by appointment only, with the ACCP Coding and Reimbursement Consultant, Diane Krier-Morrow, MBA, MPH, CCS-P, in Experience ACCP.

The following states currently have a vacancy for both the ACCP CAC representative and the ACCP CAC alternate: Colorado, Georgia, Idaho, Minnesota, Missouri, North Carolina, North Dakota, West Virginia, and Wyoming.

The following states (and districts) have a vacancy for the ACCP CAC alternate position only: Alabama, Alaska, Arizona, Arkansas, Connecticut, District of Columbia, Hawaii, Iowa, Kansas, Maryland, Michigan, Mississippi, Montana, Nebraska, Nevada, New Jersey, New Mexico, New York, Oklahoma, South Carolina, South Dakota, Tennessee, Texas, and Wisconsin.

If you are interested in applying for any of the ACCP CAC openings and/or interested in scheduling an appointment with Dr. Lurvey and Diane Krier-Morrow at CHEST 2011, please contact Marla Brchta, Manager, ACCP Health-care Practice and Reimbursement, at mbrchta@chestnet.org or (847) 498-8364.

This Month in CHEST: Editor’s Picks

By Dr. Richard B. Irwin, Master FCCP
Editor in Chief, CHEST

**AHEAD OF THE CURVE**

- *Advancing Respiratory Research.* By Dr. J. P. Riley.

- *Original Research.*

- *Survival of Chinese Patients With PAH in the Modern Treatment Era.* By Dr. R. Zhang et al.

- *Bronchoscopic and High-Resolution CT Scan Findings in Children With Chronic Wet Cough.* By Dr. K. Dours et al.

- *Physical Activity Is the Strongest Predictor of All-Cause Mortality in Patients With COPD: A Prospective Cohort Study.* By Dr. B. Wächter et al.

- *Reexamining the Recommended Follow-up Interval After Obtaining an In-Range INR Value: Results From the Veterans Affairs Study To Improve Anticoagulation.* By Dr. A. J. Rose et al.

- *Unapproved Prescription Cough, Cold, and Allergy Drug Products: Recent US FDA Regulatory Action on Unapproved Cough, Cold, and Allergy Medications.* By C. Ostroff, PharmD, et al.

- *Managing Cough in the Aftermath of the Decision of the US FDA to Remove Unapproved Prescription Cough Medications From the Market.* By Dr. R. S. Irwin, Master FCCP, and Dr. B. S. Smith.

**POINT/COUNTERPOINT**

- *Point: Is Pressure Assist-Control Preferred Over Volume Assist-Control Mode for Lung Protective Ventilation in Patients With ARDS?* By Dr. J. J. Marinelli

- *No – Dr. N. Machty, FCCP*

**EDITORIAL**

- *The Goodness of the Physician: From Hippocrates to Hi-tech.* By Sherwin Nuland, MD

- *Monday, October 24*

- *Hear physician, surgeon, teacher, medical historian, and best-selling author Sherwin Nuland, MD, discuss the role of goodness in healing, how its importance has been valued or devalued through the centuries, and its role in hi-tech medicine.*

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  - **Postgraduate Multipass Courses**
  - **Additional Saturday Courses**
  - **Saturday, October 22**
  - **General Sessions**
  - **Sunday, October 23 – Wednesday, October 26**
  - **After-CHEST Postgraduate Courses**
  - **Friday, October 28 – Saturday, October 29**

- *Learn More and Register* Early registration discounts are available through August 31.

**Keynote Address**

- **Best-Selling Author**

  - The Goodness of the Physician: From Hippocrates to Hi-tech

  - Sherwin Nuland, MD

  - Monday, October 24

- *Hear physician, surgeon, teacher, medical historian, and best-selling author Sherwin Nuland, MD, discuss the role of goodness in healing, how its importance has been valued or devalued through the centuries, and its role in hi-tech medicine.*

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- *After-CHEST Postgraduate Courses*

  - Study additional topics on neighboring islands—offered on Maui, Hawaii, and Oahu.

- **Global Focus: Integrate, Collaborate, Cooperate**

  - Increase your knowledge and ability to treat a diverse patient population.

- **ACCP Simulation Center**

  - Don’t miss the new sessions in mechanical ventilation.

- **Problem-Based Learning Sessions**

  - Work collaboratively to resolve real-world clinical problems using ACCP evidence-based guideline recommendations.

- **ACCP Self-study Clinical Library**

  - Earn additional CME in the expanded ACCP Self-study Clinical Library.

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ACCP Guideline Methodology Course

March 15-16, 2012

BY SANDRA ZELMAN LEWIS, PH.D.
Manager, Evidence-Based Guidelines and Clinical Standards

It has always been the realm of the American College of Chest Physicians (ACCP) Health and Science Policy (HSP) Committee to continually elevate the rigor of the science behind evidence-based guidelines. However there has never been as great an increase as within the last few years. As the ACCP prepared to host the Guidelines International Network (G-I-N) 2010 Conference, the HSP Committee prepared a full-day course on the ACCP Guideline Methodology. Although expected to attract far fewer, 98 people from all over the world attended, and the residual acclaim and requests for additional offerings led HSP to consider offering the course again.

Several other circumstances also promoted the idea of revising and repeating the course. Within a few months of the G-I-N conference, the ACCP hired two knowledgeable methodologists to serve on the HSP staff team. Rebecca Diekemper, MPH, and Joseph Ornelas, DC, MS, MA, created a seven-module, online self-education program on how to conduct an evidence review. Although originally intended for ACCP guideline panels, the HSP Committee urged the staff to offer these modules for further orientation of future committee members. Simultaneously, one over-arching theme of the Institute of Medicine (IOM) workshop on next steps for trustworthy clinical practice guidelines and systematic reviews was that most guideline developers needed mentoring and education from developers who are already meeting IOM standards.

Thus, the knowledge gaps were evident, and audience interest had been shown. Therefore, HSP plans to offer an expanded 2-day course on the ACCP Guideline Methodology with a new section on conducting evidence reviews, March 15-16, 2012. It will address the following major topics:

- Differences between guidelines and consensus statements
- Development and refinement of key questions
- Searching the literature
- Assessing study quality
- Systematic reviews and meta-analyses
- Developing evidence tables and evidence profiles
- Conflicts of interest
- Guideline development process
- Incorporating resource considerations into recommendations
- Incorporating values and preferences
- Guideline review and appraisal processes
- Dissemination/implementation
- Impact on quality improvement efforts, CME, and policy

Details on CME credits will be available soon.

For more information, contact Sandra Zelman Lewis, PhD, slewis@chestnet.org.
Enacting comprehensive state laws that ban smoking in workplaces and restaurants as well as raising the cigarette tax by $1 per pack across the country could bring in billions in revenue for cash-strapped states, while also saving nearly 2 million lives, according to new estimates from the American Cancer Society Cancer Action Network.

The ACS CAN released two reports that examined the public health benefits and economic savings from strengthening state antitobacco policies. In one report, researchers from the University of Illinois at Chicago looked at what would happen if the 27 states without comprehensive smoke-free laws were to enact such laws. In the second report, the same researchers considered the impact if all 50 states and the District of Columbia were to adopt a $1 per pack increase in the cigarette excise tax.

“The bottom line is that strong tobacco control policies are a win-win for state legislators, for the states themselves, and [for] their constituents,” said John R. Seffrin, Ph.D., chief executive officer of ACS CAN.

Currently, 23 states and the District of Columbia have enacted comprehensive laws that ban smoking in all bars, restaurants, and workplaces. The remaining 27 states have either less-comprehensive laws or no laws at all in this area. But when the researchers considered the impact if these 27 states were to adopt comprehensive smoking bans, they found that more than 1 million adults would quit smoking, nearly 400,000 children would never start smoking, and smoking-related deaths would fall by 624,000.

On the economic side, those 27 states would see a savings of about $316 million from lung cancer treatment, $875 million from heart attack and stroke treatment, and $128 million from smoking-related pregnancy treatment. And the researchers estimated that Medicaid programs in those 27 states would save a collective $42 million.

The report on tobacco taxes found similar public health and financial gains: if a $1 per pack tax increase were enacted around the country. Such a tax would result in 1.4 million adults quitting smoking, 1.69 million children never starting to smoke, and 1.32 million fewer people dying from smoking-related causes. States also could benefit from both decreases in Medicaid spending and increased revenue. The report estimated that the tax would cut Medicaid spending by about $1.46 million across the states, and would bring in $8.62 billion in new state revenue.

Dr. Seffrin said that the results are attainable. An increasing number of states are adopting smoke-free laws and nearly all the states have increased cigarette excise taxes in recent years.

But he noted the ACS CAN is concerned that the tobacco industry is working to erode current tobacco-control laws at the state level. For example, there have been efforts in several states to add exemptions to the smoke-free laws.

Graphic Cigarette Packaging to Debut Next Month

BY MICHÉLE G. SULLIVAN
Elsevier Global Medical News

The Food and Drug Administration unveiled the finalized tobacco warning images that will appear on every package of cigarettes by 2012—graphic photos and drawings intended to educate consumers about the dangers of smoking.

The images, set to debut in stores this September, are required by the 2009 Tobacco Control Act, according to FDA spokesman Jeffrey Ventura, who added that these are the first changes to cigarette pack warnings in 25 years. By Oct. 22, 2012, cigarette manufacturers will no longer be able to distribute cigarettes for sale in the United States unless they display these warnings.

The law required the warnings to cover the top half of the front and back of cigarette packs and 20% of cigarette advertisements, and they must contain color graphics depicting the negative health consequences of smoking.

“This is something Congress wanted to happen and mandated that the FDA carry out,” Mr. Ventura said in an interview. Based on a study of 18,000 smokers conducted for the FDA by RTI International, federal officials said they firmly believe that visually communicating smoking’s harm will deter cigarette consumption over the long run.

The images include photos of tobacco-related diseases: lungs beside healthy lungs, a corpse in a casket, a man exhaling smoke through a tracheostomy, lip cancer, and mothers blowing smoke into infants’ faces. One positive image shows a burly man exposing a T-shirt saying, “I Quit.”

Mr. Ventura said the images were selected after the consumer study involving smokers aged 15-50 years. After viewing each of the images, subjects rated their emotional and cognitive responses, their ability to recall the images, and their opinions on whether the pictures could alter their beliefs about the danger of smoking and the desire to buy tobacco products and quitting smoking.

The study concluded, however, that none of the images were significantly related to an increased likelihood of quitting smoking within the next 30 days, or the likelihood of smoking a year after viewing the images. Thus, the report noted, the campaign is more likely to exert a long-term behavioral impact than any immediate effects.

“Eliciting strong emotional and cognitive reactions to the graphic cigarette warning label enhances recall and processing of the health warning, which helps ensure that the warning is better processed, understood, and remembered,” the study said. “As attitudes and beliefs change, they eventually lead to changes in intentions to quit or start smoking and then later to lower smoking initiation and successful cessation.”

The time scale on which this behavior change process occurs is largely unknown in the context of the impact of exposure to graphic warning labels on smoking behaviors, but the effects on behavior change are unlikely to be immediate or short-term.

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CMS Proposes Looser E-Prescribing Rules

BY ALICIA AULT
Elsevier Global Medical News

The Centers for Medicare and Medicaid Services has proposed modifying the rules for e-prescribing so that more physicians could claim exemptions from the criteria and therefore avoid being penalized in 2012.

In a conference call with reporters, agency officials said the change in the e-prescribing program was in response to indications from providers and professional societies that many prescribers might not be able to meet the requirements of the current incentive program.

“Today’s rule demonstrates that CMS is willing to work cooperatively with the medical professional community to encourage participation in electronic prescribing,” Dr. Patrick Conway, chief medical officer at CMS and director of the agency’s Office of Clinical Standards and Quality, said in a statement.

“These proposed changes will continue to encourage adoption of electronic prescribing while acknowledging circumstances that may keep health professionals from realizing the full potential of these systems right away,” he said.

Under the current incentive program, which was established in the Medicare Improvements for Patients and Providers Act of 2008, eligible prescribers were due to get a 1% bonus payment for 2011 and 2012 and a 0.5% bonus in 2013. For prescribers who did not prescribe enough drugs in the first place, who are barred by law from issuing enough electronic drug orders (such as prohibited B/C/B-controlled drugs); or prescribe drugs only during patient encounters that don’t count under the program (such as many surgeons and critical care specialists). Practices will also be able to avoid penalties if they did not e-prescribe by June 30, 2011, because they were planning instead to adopt and use an EMR in 2011 to qualify for the meaningful use bonuses.

Dr. Stuart Garay, FCCP, comments: Medicare defines an eligible professional requiring e-prescribing as meeting the following three criteria: 1) the physician has prescribing privileges as of June 30, 2011; 2) the physician has at least 100 instances of eligible patient encounters for e-prescribing, such as an office evaluation and management visit, between Jan. 1, 2011, and June 30, 2011; and 3) the physician has at least 10% of total Medicare charges associated with eligible patient encounters.

This is an important proposed revision to the Medicare e-prescribing rules. According to CMS, 100,000-200,000 physicians and other health care providers will be eligible for hardship exemptions. A special website will be available to file by Oct. 1, 2011, for one of the several exemption categories. These new rules better align the requirements of the e-prescribing and EMR programs. In addition, the exemptions will help physicians who don’t prescribe enough drugs in the first place.

For more details please contact Kem Toller at (410) 286-1644 or kem@annapolispulmonary.com.

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The use of Tigecycline in both treatment (half of half) or prophylaxis, and therapy to all age groups is recommended as the \textit{toxicity is generally mild and not related to age}.

\textit{Treatment of complicated intra-abdominal infection is usually considered to be successful when the absolute neutrophil count returns to baseline or at least 2000/mm$^3$, clinical signs and symptoms of infection resolve, and when no evidence of abscess exists.}\n
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TYGACIL does not cover Pseudomonas aeruginosa.

TYGACIL is indicated for the treatment of adults with:

- Complicated skin and skin structure infections caused by Escherichia coli, Enterococcus faecalis (vancomycin-susceptible isolates), Staphylococcus aureus (methicillin-susceptible and -resistant isolates), Streptococcus agalactiae, Streptococcus anginosus grp. (includes S. anginosus, S. intermedius, and S. constellatus), Streptococcus pyogenes, Enterobacter cloacae, Klebsiella pneumoniae, and Bacteroides fragilis
- Complicated intra-abdominal infections caused by Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Enterococcus faecalis (vancomycin-susceptible isolates), Staphylococcus aureus (methicillin-susceptible and -resistant isolates), Streptococcus anginosus grp. (includes S. anginosus, S. intermedius, and S. constellatus), Bacteroides fragilis, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides vulgatus, Clostridium perfringens, and Peptostreptococcus micros
- Community-acquired bacterial pneumonia caused by Streptococcus pneumoniae (penicillin-susceptible isolates), including cases with concurrent bacteremia, Haemophilus influenzae (beta-lactamase negative isolates), and Legionella pneumophila

Important Safety Information

- TYGACIL is contraindicated in patients with known hypersensitivity to tigecycline
- Anaphylaxis/anaphylactoid reactions have been reported with nearly all antibacterial agents, including tigecycline, and may be life-threatening. TYGACIL should be administered with caution in patients with known hypersensitivity to tetracycline-class antibiotics
- Isolated cases of significant hepatic dysfunction and hepatic failure have been reported in patients being treated with tigecycline. Some of these patients were receiving multiple concomitant medications. Patients who develop abnormal liver function tests during tigecycline therapy should be monitored for evidence of worsening hepatic function. Adverse events may occur after the drug has been discontinued
- The safety and efficacy of TYGACIL in patients with hospital-acquired pneumonia have not been established
- An increase in all-cause mortality has been observed across phase 3 and 4 clinical studies in TYGACIL-treated patients versus comparator-treated patients. The cause of this increase has not been established. This increase in all-cause mortality should be considered when selecting among treatment options
- TYGACIL may cause fetal harm when administered to a pregnant woman
- The use of TYGACIL during tooth development may cause permanent discoloration of the teeth. TYGACIL should not be used during tooth development unless other drugs are not likely to be effective or are contraindicated
- Acute pancreatitis, including fatal cases, has occurred in association with tigecycline treatment. Consideration should be given to the cessation of the treatment with tigecycline in cases suspected of having developed pancreatitis
- Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including TYGACIL, and may range in severity from mild diarrhea to fatal colitis
- Monotherapy should be used with caution in patients with clinically apparent intestinal perforation
- TYGACIL is structurally similar to tetracycline-class antibiotics and may have similar adverse effects. Such effects may include: photosensitivity, pseudotumor cerebri, and anti-arachidonic action (which has led to increased BUN, azotemia, acidosis, and hyperphosphatemia). As with tetracyclines, pancreatitis has been reported with the use of TYGACIL
- To reduce the development of drug-resistant bacteria and maintain the effectiveness of TYGACIL and other antibacterial drugs, TYGACIL should be used only to treat infections proven or strongly suspected to be caused by susceptible bacteria. As with other antibacterial drugs, use of TYGACIL may result in overgrowth of non-susceptible organisms, including fungi
- The most common adverse reactions (incidence >5%) are nausea, vomiting, diarrhea, infection, headache, and abdominal pain
- Prothrombin time or other suitable anticoagulant test should be monitored if TYGACIL is administered with warfarin
- Concurrent use of antibacterial drugs with oral contraceptives may render oral contraceptives less effective
- The safety and effectiveness of TYGACIL in patients below age 18 and lactating women have not been established

Please see brief summary of Prescribing Information on adjacent page.