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SHERRY BOSCHERT/ELSEVIER GLOBAL MEDICAL NEWS

High-dose corticosteroids taken only during respiratory illness were effective in young children, Dr. Leonard B. Bacharier said.

Intermittent Tx Works For Wheezing Toddlers

BY SHERRY BOSCHERT
Elsevier Global Medical News

SAN FRANCISCO – Intermittent courses of high-dose inhaled budesonide were as effective and as safe as daily low-dose inhaled budesonide in wheezing toddlers but exposed them to a lower cumulative dose of the corticosteroid in a year-long study of 278 children.

The two groups did not differ significantly in the frequency of exacerbations that required systemic corticosteroids, the frequency or severity of respiratory tract illness, the number of urgent or emergent visits for care, or other efficacy and safety measures, Dr. Leonard B. Bacharier and his associates reported at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

Children in the daily low-dose budesonide group, however, were exposed to more than three times the cumulative dose of budesonide, compared with the intermittent high-dose therapy group – 150 mg vs. 46 mg.

The multicenter, randomized, double-blind, placebo-controlled trial, called the Maintenance Versus Intermittent Inhaled Steroids in Wheezing Toddlers (MIST) study, is the last of eight clinical trials performed by the National Heart, Lung, and Blood Institute's Childhood Asthma Research and Education Network.

The NHLBI's 2007 "Expert Panel Report 3: Guidelines for Diagnosis and Management of Asthma" recommended using daily low-dose inhaled corticosteroids to treat children who have a positive modified Asthma Predictive Index.

The MIST study is the first to compare the currently recommended daily low-dose regimen with the intermittent high-dose regimen, said Dr. Bacharier of Washington University, St. Louis.

On the basis of the MIST results, Dr. Bacharier and his associates recommended instead that clinicians consider using intermittent high-dose inhaled corticosteroids in the subset of children identified in the MIST

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EGFR Testing in Advanced Lung Cancer Urged

Mutations predict treatment response.

BY DIANA MAHONEY
Elsevier Global Medical News

Testing for epidermal growth factor receptor mutations is an important step in the evaluation process for systemic therapy in patients with metastatic or recurrent non–small cell lung cancer, according to updated recommendations issued by the American Society of Clinical Oncology and the National Comprehensive Cancer Network.

ASCO issued a provisional clinical opinion (PCO) that patients with advanced non–small cell lung cancer (NSCLC) who are being considered for treatment with one of the tyrosine kinase inhibitors (TKIs) that target the epidermal growth factor receptor (EGFR) should undergo EGFR-mutation testing.

Oncologists have learned that NSCLC is "really a collection of genetically distinct diseases," ASCO's PCO panel cochair Dr. Vicki L. Keedy of Vanderbilt-Ingram Cancer Center in Nashville, Tenn., said in a press release. The goal is to "treat patients with drugs that target the molecular drivers of their specific tumors rather than using a one-size-fits-all approach."

The NCCN earlier updated its clinical management guidelines to include a category 1 recommendation that EGFR testing should be undertaken after histologic diagnosis of adenocarcinoma, large cell carcinoma, or undifferentiated carcinoma.

The NCCN recommendation does not extend to patients with squamous cell lung cancer because the incidence of EGFR mutation in this subgroup is less than 3.6%, Dr. David S. Ettinger, FCCP, said at the organization's annual conference.

Both groups based their endorsements on studies

See **EGFR** • *page 14*

INSIDE

Airline Travel Can Trip Up Patients

BY DAMIAN McNAMARA
Elsevier Global Medical News

FORT LAUDERDALE, FLA. – Your patients with cystic fibrosis or other pulmonary conditions may ask you if and when it's safe for them to fly on an airplane.

How you respond can depend in part on their travel history, how long they will be exposed to increased cabin pressure, and if they are immunocompromised or have other risk factors for infection that are related to airborne pathogens, Dr. Susan L. Millard, FCCP, said.

Severe respiratory insufficiency, right heart failure or hemodynamic instability, and active pneumothorax are absolute contraindications to air travel, according to 30 experts who wrote a consensus statement for traveling with cystic fibrosis (J. Cyst. Fibros. 2010; 9:385-99).

These first-ever European recommendations address preparations for travel (for example, vaccinations and packing medication), important considerations during travel,

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Don't Judge Asthma Control By Lung Function Alone

BY DOUG BRUNK
Elsevier Global Medical News

SAN FRANCISCO – Lung function alone is a poor marker of asthma control in children, results from a large retrospective analysis showed.

"Physicians should use all components of the 2007 National Asthma Education and Prevention Program Expert Report 3 guidelines, asking questions to patients not only about daytime and nighttime symptoms, but doing lung function testing as well," Dr. Edward K. Hu advised during a poster session at the annual meeting of the American Academy of Allergy, Asthma, and Immunology. "Even [among] those patients who are enrolled in a disease management program, there is still going to be a large minority who are going to be uncontrolled."

VITALS

Major Finding: When lung function alone was used as a marker of asthma control in children, 17% exhibited asthma that was not well controlled, and 5% asthma that was poorly controlled. Consideration of impairment and risk resulted in a downgrade of asthma control in an additional 22%.

Data Source: A study of 453 children enrolled in an asthma management program.

Disclosures: Dr. Hu said that he had no relevant financial disclosures.

Dr. Hu, a fellow in the division of allergy and immunology at the Los Angeles County/University of Southern California Medical Center, Los Angeles, and his associates studied 453 children aged 5-18 years who were enrolled in an asthma management program and made a total of 886 follow-up visits. Initial analysis defined asthma control based solely on lung function. Secondary analysis included all components of asthma control based on the 2007 National Asthma Education and Prevention Program Expert Report 3, which included impairment and risk. Of the 453 children, 61% were male and 83% were Hispanic.

At baseline more than one-quarter of patients (29%) had intermittent disease, 21% had mild persistent disease, 25% had moderate persistent disease, and 25% had severe persistent disease.

Dr. Hu reported that when lung function alone was used, 17% of children exhibited asthma that was not well controlled, and 5% exhibited asthma that was poorly controlled. Inclusion of impairment and risk resulted in a downgrade of asthma control in another 22%.

The researchers also found that boys aged 8-11 years were significantly more likely than girls that age to have with normal lung function and uncontrolled disease due to other factors (24% vs. 15%). ■

IN THIS ISSUE

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More H1N1 Seen in Children With Asthma

BY DOUG BRUNK
Elsevier Global Medical News

SAN FRANCISCO – During 2009's peak influenza season, children with asthma were nearly twice as likely to be infected with the novel H1N1 influenza virus, compared with other viruses, according to results from a prospective single-center study.

VITALS

Major Finding: During peak flu season, the incidence of H1N1 influenza infection was 39% among asthmatic children and 25% among their nonasthmatic counterparts (not statistically significant, odds ratio 1.9, $P = .06$). After adjustment for race, sex, and allergic sensitization, the difference became statistically significant (OR 3.5, P less than .002).

Data Source: Single-center study of 161 children aged 4-12 years.

Disclosures: The study was supported by grants from the National Institutes of Health. Dr. Kloepfer said she had no other relevant financial disclosures.

In addition, H1N1 influenza infection caused increased severity of both cold and asthma symptoms, compared with other infections.

Although reasons for the association remain unclear, "this really proves that asthmatics need to be vaccinated for the flu, because we can see that they're more susceptible to be infected when they're exposed, and they're more susceptible to have loss of asthma control when they get it," lead investigator Dr. Kirsten M. Kloepfer said in an interview during a poster session at the annual meetingof the American Academy of Allergy, Asthma, and Immunology.

Dr. Kloepfer, a fellow in allergy and clinical immunology at the University of Wisconsin, Madison, and her associates evaluated 161 children aged 4-12 years who provided at least six of eight consecutive weekly nasal samples between Sept. 5 and Oct. 24, 2009. Of these 161 children, 94 had asthma and 67 did not. Their mean age was 9 years, and 60% were boys.

Dr. Kloepfer reported that the incidence of H1N1 influenza infection was 39% in asthmatics and 25% in nonasthmatics, a difference that was not statistically significant, with an odds ratio of 1.9 ($P = .06$).

However, after adjustment for race, sex, and allergic sensitization, the difference became statistically significant, increasing to an OR of 3.5 (P less than .002).

The incidence of human rhinovirus was statistically similar between the two groups (89% in asthmatics vs. 93% in nonasthmatics), as was the incidence of other viral infections (37% vs. 42%).

Both asthmatics and nonasthmatics reported significant increases in moderate and severe cold symptoms with H1N1, compared with rhinovirus (63% vs. 28%). Also, a significantly higher proportion of moderate to severe asthma was seen in H1N1 patients, compared with rhinovirus patients (48% vs. 23%). This association held true for severe asthma symptoms as well (19% vs. 4%). Dr. Kloepfer acknowledged certain limitations of the study, including its single-center design, the fact that it included only children aged 4-12 years, and the fact that it lasted only 8 weeks. ■

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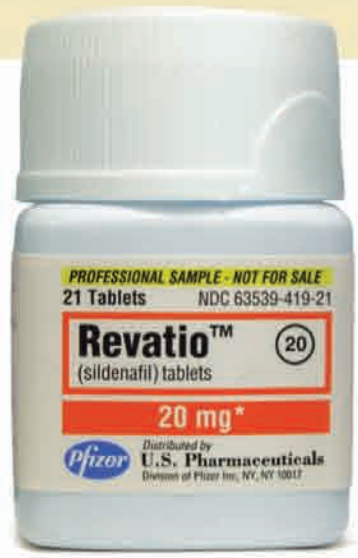

Important Safety Information

Do not use REVATIO in patients taking organic nitrates in any form, either regularly or intermittently. Consistent with its known effects on the nitric oxide/cGMP pathway, sildenafil was shown to potentiate the hypotensive effects of nitrates.

Before starting REVATIO, physicians should carefully consider whether their patients with underlying conditions could be adversely affected by the mild and transient vasodilatory effects of REVATIO on blood pressure. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD) and administration of REVATIO to these patients is not recommended. Should signs of pulmonary edema occur when sildenafil is administered, the possibility of associated PVOD should be considered.

Caution is advised when PDE5 inhibitors, such as REVATIO, are administered with α-blockers as both are vasodilators with blood pressure lowering effects.

In PAH patients, the concomitant use of vitamin K antagonists and REVATIO resulted in a greater incidence of reports of bleeding (primarily epistaxis) versus placebo. The incidence of epistaxis was higher in patients with PAH secondary to CTD (sildenafil 13%, placebo 0%) than in PPH patients (sildenafil 3%, placebo 2%).

Co-administration of REVATIO with potent CYP3A4 inhibitors, eg, ketoconazole, itraconazole, and ritonavir, is not recommended as serum concentrations of sildenafil substantially increase. Co-administration of REVATIO with CYP3A4 inducers, including bosentan; and more potent inducers such as barbiturates, carbamazepine, phenytoin, efavirenz, nevirapine, rifampin, and rifabutin, may alter plasma levels of either or both medications. Dosage adjustment may be necessary.

Non-arteritic anterior ischemic optic neuropathy (NAION) has been reported post-marketing in temporal association with the use of PDE5 inhibitors for the treatment of erectile dysfunction, including sildenafil.

It is not possible to determine if these events are related to PDE5 inhibitors or to other factors. Physicians should advise patients to seek immediate medical attention in the event of sudden loss of vision while taking PDE5 inhibitors, including REVATIO.

Sudden decrease or loss of hearing has been reported in temporal association with the intake of PDE5 inhibitors, including REVATIO. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE5 inhibitors, including REVATIO.

REVATIO should be used with caution in patients with anatomical deformation of the penis or patients who have conditions which may predispose them to priapism.

The effectiveness of REVATIO in pulmonary hypertension (PH) secondary to sickle cell anemia has not been established. In a small, prematurely terminated study of patients with PH secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported by patients who received REVATIO than by those randomized to placebo.

REVATIO contains sildenafil, the same active ingredient found in VIAGRA®. Combinations of REVATIO with VIAGRA or other PDE5 inhibitors have not been studied. Patients taking REVATIO should not take VIAGRA or other PDE5 inhibitors.

Patients with the following characteristics did not participate in the preapproval clinical trial: patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months, unstable angina, hypertension (BP >170/110), retinitis pigmentosa, or patients on bosentan. The safety of REVATIO is unknown in patients with bleeding disorders and patients with active peptic ulceration. In these patients, physicians should prescribe REVATIO with caution.

The most common side effects of REVATIO (placebo-subtracted) were epistaxis (8%), headache (7%), dyspepsia (6%), flushing (6%), and insomnia (6%). Adverse events of REVATIO injection were similar to those seen with oral tablets.

The most common side effects of REVATIO (placebo-subtracted) as an adjunct to intravenous epoprostenol were headache (23%), edema (14%), dyspepsia (14%), pain in extremity (11%), diarrhea (7%), nausea (7%), and nasal congestion (7%).

Indication

REVATIO is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise ability and delay clinical worsening. Delay in clinical worsening was demonstrated when REVATIO was added to background epoprostenol therapy. Studies establishing effectiveness included predominantly patients with NYHA Functional Class II-III symptoms and etiologies of primary pulmonary hypertension (71%) or pulmonary hypertension associated with connective tissue disease (25%). The efficacy of REVATIO has not been adequately evaluated in patients taking bosentan concurrently.

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Study Finds LABA Combo Safe for Children

BY DOUG BRUNK
Elsevier Global Medical News

SAN FRANCISCO – Adding long-acting beta-agonists to a regimen consisting of inhaled corticosteroids did not increase the rate of admissions to the pediatric intensive care unit, results from a year-long study showed.

"This supports the guidelines from the National Asthma Education and Prevention Program," Dr. Tammy S. Jacobs said in an interview during a poster session at the annual meeting of the American Academy of Allergy, Asthma, and Immunology. "When you fail to have adequate control with inhaled corticosteroids alone, long-acting beta-agonists can be a very good medication to add."

While results from the U.K. Serevent Nationwide Surveillance study and the U.S. Salmeterol Multicenter Asthma Research Trial suggested that long-acting beta-agonists (LABAs) increase the risk of asthma-related mortality, neither trial was adequately powered to study the safety of LABAs when used in conjunction with inhaled corticosteroids (ICS), said Dr. Jacobs, a resident at Children's Hospital of Pittsburgh. In an effort to evaluate the impact of LABA use in conjunction with inhaled corticosteroids on the risk of near-fatal asthma in children, she and her associates reviewed the medical charts of 363 children aged 4-18 years who were admitted for asthma exacerbations to

COMMENTARY

Dr. Burt Lesnick, FCCP, comments: Although this is a small study, it does add to the accumulation of data regarding safety. These findings were published in abstract form. It would be interesting to know the ethnic breakdown of the participants when the full article is submitted for publication.

Children's Hospital of Pittsburgh in 2005.

Cases and controls were determined by pediatric intensive care (PICU) and floor admissions, respectively. Exposure was defined by LABA use in combination with ICS vs. ICS alone.

After excluding patients with non–asthma-indicated admissions, complicated pneumonias, debilitating comorbid disorders, and multiple admissions, 85 PICU admissions and 96 floor admissions were included in the final analysis. The mean age of patients was 9 years, 54% were male, and 51% were white.

Dr. Jacobs reported that the use of LABA in conjunction with ICS did not significantly increase the risk of PICU admissions (odds ratio, 1.07), compared with ICS alone. After the researchers adjusted for demographics, asthma severity, history of PICU admissions, and concurrent infection, they found that the use of LABA in conjunction with ICS may have decreased the risk of PICU admission, compared with ICS alone (OR, 0.85). No deaths occurred during the study period.

"Although this [study] does not directly evaluate increase in mortality (as in previous trials), risk of ICU admission may actually be a more clinically relevant outcome to evaluate LABA safety," the researchers concluded in their poster. "Findings are generalizable to a population of children with relatively higher-risk asthma/poorer asthma control since all subjects were admitted, and no outpatient subjects were included."

Dr. Jacobs acknowledged certain limitations of the study, including the fact that it was a retrospective chart review with the potential for missing data.

She said that she had no relevant financial conflicts to disclose. ■

Take as Needed

Toddlers • *from page 1*

study, who were not the most severe asthma cases. They suggested starting a 7-day course of high-dose budesonide early during respiratory tract illnesses in wheezing children who have a positive modified Asthma Predictive Index, have had at least one exacerbation in the past year, use albuterol less than 3 days per week, and have had no more than one night awakening in the prior 2 weeks.

The study enrolled children 12-53 months of age. All children had a history of at least four wheezing episodes in the prior year (or at least three if they'd had 3 months or more of asthma controller therapy) and a positive modified Asthma Predictive Index. Each child also had at least one severe exacerbation that required systemic corticosteroids or an unscheduled urgent or emergent visit or hospitalization in the previous year.

The study excluded children who had more than two hospitalizations for wheezing or more than six courses of oral corticosteroids. During a 2-week run-in period, all children used a nebulized placebo nightly and albuterol as needed; children who had persistent symptoms or did not follow the protocol for more than 25% of days also were excluded.

The children were then randomized for 52 weeks of therapy. The daily low-dose budesonide group used 0.5 mg of nebulized budesonide once daily at night except during respiratory tract illness, when they switched to nebulized placebo in the morning and 0.5 mg of budesonide at night for 7 days. The intermittent high-dose budesonide group used nebulized placebo once daily at night except during respiratory tract illness, when they used 1 mg of budesonide in the morning and at night for 7 days.

Previous studies have shown that daily inhaled corticosteroids have "a small but statistically significant class effect on reducing linear growth in preschool-aged children," which was a main reason for studying the intermittent-therapy alternative, Dr. Bacharier said.

In the MIST study, children in the daily-therapy group grew an average of 7.76 cm, compared with 8.01 cm in the intermittent-therapy group, but the 0.25-cm greater growth with intermittent therapy was not statistically significant.

There were no significant differences between groups in baseline characteristics, adherence to therapy, declines in exhaled nitric oxide, time to first exacerbation, or time to treatment failure.

The NHLBI funded the study. AstraZeneca provided the budesonide and placebo for the study. Dr. Bacharier has been a consultant for AstraZeneca (which markets budesonide), Merck, and Novartis, and has received honoraria from GlaxoSmithKline. ■

COMMENT

Dr. Burt Lesnick, FCCP, comments: Pediatric providers should pay close attention to these results. Ultimately, our clinical practice may be altered.

Pediatric Airway Clearance Strategies Lack Data

These devices 'may be better than doing nothing at all.'

BY DAMIAN McNAMARA
Elsevier Global Medical News

FORT LAUDERDALE, FLA. – Despite a lack of definitive evidence, airway clearance strategies are commonly employed in children with cystic fibrosis and other lung diseases, Dr. Veda L. Ackerman said.

"Unfortunately, we don't really know very much about airway clearance. We do it a lot, but we don't have a lot of data," Dr. Ackerman said at a seminar on pediatric pulmonology sponsored by the American College of Chest Physicians and the American Academy of Pediatrics.

For instance, the only pediatric study comparing airway clearance to no such therapy was published in 1983 and assessed eight patients with cystic fibrosis (J. Pediatr. 2003;103:538-42).

"Intuitively and intellectually, airway clearance makes a lot of sense. But [it is important to] think about whether we are helping or hurting when we prescribe airway clearance," said Dr. Ackerman, a pediatric intensivist at Riley Hospital for Children and a pediatric pulmonologist in private practice in Indianapolis.

Oxygen desaturation, gastroesophageal reflux, aspiration, hyperventilation, and "guilt for the family from lack of adherence" are potential adverse events associated with prescription of airway clearance, Dr. Ackerman said.

There are "no data to support the use of one airway clearance technique over the other," Dr. Ackerman said. Chest physiotherapy (CPT), positive expiratory pressure (PEP) valve, Cardinal Health's Flutter device, Smiths Medical's Acapella system, Medical Acoustics' Lung Flute device, airway clearance vests, and Smiths Medical's EzPAP device are among the options.

No definitive data exist to support use of CPT in an asymptomatic child with cystic fibrosis, Dr. Ackerman said. This patient population is prone to adverse events, especially gastroesophageal reflux with or without aspiration. CPT also requires a significant time commitment on the part of families. Despite these concerns, "I still do recommend it" for some patients.

Airway clearance devices "jiggle, shake, or use sound waves to loosen mucus off the airway walls so secretions can be coughed up," Dr. Ackerman said. Success with these devices is often technique dependent.

The PEP valve is portable, takes 10-15 minutes to clear the airway, and can be used with aerosolized medications. However, Dr. Ackerman's institution uses the Flutter "much more than the PEP valve," she said. This device "tends to be used for families who cannot put time into CPT or when the child goes to Grandma's or on a sleepover." The device loosens mucus through expiratory oscillation, so it may be less effective at lower airflows, such as those used for small children or patients with more severe lung disease. The device has to be held at a precise angle to maximize oscillation, she added. Each use of the Flutter device takes about 10-15 minutes.

The Acapella system combines the benefits of the PEP valve and airway vibrations to mobilize secretions, Dr. Ackerman said. The mechanism of action is similar to that of the Flutter, except that the Acapella has a valve-magnet device to interrupt expiratory flow and thus can be used at any angle.

"All of these devices cost less than $100," Dr. Ackerman said. "These may – and I said may – be better than doing nothing at all."

Contraindications to the PEP valve, Flutter, and Acapella include pneumothorax, hemoptysis, and esophageal varices. Lung surgery is another contraindication, Dr. Ackerman said, because use of airway-clearance devices can cause an air leak or can break down an anastomosis site. A pulmonary embolus is another contraindication, but "fortunately we do not see this often in pediatrics." A perforated ear drum is also a contraindication to these airway devices "because it causes pain."

The Lung Flute uses a different strategy (acoustic waves) to increase mucociliary clearance. It vibrates the chest in a way that is similar to the way a reed instrument vibrates when it's played, Dr. Ackerman said. "There are no pediatric data, but it is cheap and easy to use." The Lung Flute is used more commonly for patients with chronic obstructive pulmonary disorder and not as much in cystic fibrosis.

Airway clearance vests deliver pulses of air pressure to the chest wall. The vest loosens mucus through shearing at the air/mucus interface, and compression causes clearance through repetitive peak expiratory flows that expel mucus like small coughs.

"You should not get compression of the airway itself; only the chest wall is compressed," Dr. Ackerman said. In contrast, "if you blow hard enough with the Acapella, Flutter, or PEP, you could get airway collapse." An airway clearance vest costs approximately $10,000, and obtaining insurance approval can be difficult; reimbursement policies vary from state to state.

The EzPAP device clears airways through positive airway pressure in a way that is similar to intermittent positive pressure breathing. It is approved by the Food and Drug Administration for lung expansion therapy and the prevention and treatment of atelectasis. Although no peer-reviewed data are available, many children are using EzPAP because respiratory therapists believe in this device, Dr. Ackerman said.

For more information, Dr. Ackerman recommended the American College of Chest Physicians' Evidence-Based Guidelines for Nonpharmacologic Airway Clearance Therapies (Chest 2006;129:250S-9S), which were published in 2006 but are still applicable in 2011, she added.

She said she had no relevant financial disclosures. ■

Farm Children Less Likely to Develop Asthma

BY MARY ANN MOON
Elsevier Global Medical News

Children living on farms have a lower prevalence of asthma, likely due to a protective effect of their early exposure to a greater variety of environmental bacteria and fungi compared with what other children are exposed to, according to a recent report.

VITALS

Major Finding: Children who live on a farm have a lower prevalence of asthma, compared with other children (odds ratios of 0.49 and 0.76 in two studies).

Data Source: An epidemiologic analysis of two observational studies involving more than 16,000 school-aged children in rural and suburban areas of central Europe.

Disclosures: The analysis was funded by the Deutsche Forschungsgemeinschaft and the European Commission. Dr. Ege reported having a planned patent on asthma-protective bacteria. His associates reported ties to GlaxoSmithKline, Novartis, Protectimum, and ALK.

In an epidemiologic analysis of data from two large observational studies of school-aged children in rural areas of central Europe, environmental samples from farmhouses showed a greater diversity of microbes than those from other homes.

"The central finding of this analysis was the inverse association of the diversity scores with asthma [prevalence], which was not confounded by living on a farm," said Dr. Markus J. Ege of University Children's Hospital, Munich, and his associates.

The analysis included data from a cross-sectional survey of 6,963 school children (aged 6-13 years), approximately half of whom lived on farms and the other half of whom lived in rural and suburban areas of Bavaria. Dust samples were collected from the mattresses of a randomly selected subgroup of 489 of the participants. Data also were obtained on the children's respiratory and allergic symptoms, medical diagnoses, and potential confounders.

Children living on farms had a lower prevalence of asthma than did other children, with an adjusted odds ratio of 0.49. The percentage of dust samples that were positive for bacteria was significantly higher among farm dwellers, and the risk of asthma decreased significantly with an increasing number of detectable bands of bacterial DNA.

The analysis also included data from a second cross-sectional study involving 9,668 children attending elementary schools in rural areas of southern Germany, Switzerland, and Austria. Airborne dust samples were collected from the children's bedrooms.

Again, children living on farms had a lower prevalence of asthma than did other children, with an odds ratio of 0.76. All bacterial and fungal taxa cultured from the dust samples were more prevalent among children living on farms than among other children, and the risk of asthma decreased significantly with an increasing number of fungal taxa, Dr. Ege and his colleagues said (N. Engl. J. Med. 2011;364:701-9).

In both studies, the diversity of microbes explained a substantial portion of the protective effect of the farming environment on asthma risk.

"Our methods do not allow us to identify specific microbes that may confer protection, but they have allowed us to identify broad families of species within microbial taxa that could be responsible for the effect of the farming environment. The challenge will be to identify these species with the precision needed to allow specific tests of the relationship between microbial exposure and protection against asthma," the investigators noted.

COMMENTARY

Dr. Burt Lesnick, FCCP, comments: This study adds to a growing body of evidence that farm exposure in children is associated with a lower prevalence of asthma. Additional work in this area has identified genetic polymorphisms in CD 14 that accentuate this effect. It is unclear if endotoxin (and bacterial) exposure might be helpful in all children or only those with a specific genotype.

The analysis also could not determine the mechanism underlying this protective effect – how the diversity of microbial stimuli protects against asthma – but the researchers agreed with the prevailing view that perhaps micro-organisms trigger the innate immune system, which then bolsters resistance to asthma.

An alternative explanation may be that exposure to a broad rather than a narrow range of micro-organisms may prevent colonization of the lower airways with harmful bacteria. "Balanced colonization of the airways may parallel the beneficial effects of a diverse microbiome at other surfaces, such as the gut and skin," they added. ■

IV Hydrocortisone Cut Pneumonia in Trauma Patients

BY MARY ANN MOON
Elsevier Global Medical News

Providing intravenous stress-dose hydrocortisone for 1 week reduced the rate of hospital-acquired pneumonia among intubated patients with multiple trauma, according to a report in JAMA.

The treatment also decreased the number of days on mechanical ventilation, the incidence of acute respiratory distress syndrome, and the length of stay in the ICU, said Dr. Antoine Roquilly of the departments of anesthesiology and intensive care medicine, University Hospital of Nantes (France), and his associates.

The researchers evaluated stress-dose hydrocortisone therapy in a double-blind clinical trial because it was thought the treatment might "attenuate the overwhelming inflammatory response without immunosuppression, restoring an adequate immune response to infection." They postulated that this would be helpful in reducing the prevalence of hospital-acquired pneumonia, the major cause of infection in trauma patients.

A total of 150 intubated patients with multiple trauma who were older than 15 years and were expected to require mechanical ventilation for more than 48 hours were enrolled at seven ICUs in France over a 3-year period. Half were randomly assigned to receive stress-dose (200 mg/day) IV hydrocortisone and half to receive placebo infusions for 7 days.

The study's primary end point was the rate of hospital-acquired pneumonia within 28 days. The subjects were evaluated twice daily for the development of pneumonia during the first month in the ICU.

Of the 73 patients treated with hydrocortisone who completed the trial, 26 (36%) developed pneumonia, a significantly lower rate than the 39 (51%) of 76 placebo patients who developed pneumonia. The findings were similar in an intention-to-treat analysis, Dr. Roquilly and his colleagues said (JAMA 2011;305:1201-9).

When the analysis was restricted to the 103 patients who showed corticosteroid insufficiency at baseline, the results were similar: a 36% rate of pneumonia with hydrocortisone therapy and a 54% rate with placebo.

"Subgroup analysis suggests that hydrocortisone was particularly effective for patients with traumatic brain injury," the investigators noted.

Among those with traumatic brain injury who presented with corticosteroid insufficiency, 41% in the hydrocortisone group developed pneumonia vs. 71% in the placebo group.

The short duration of exposure to IV hydrocortisone did not adversely affect the 47 patients who did not have corticosteroid insufficiency at baseline, they added.

Patients who received hydrocortisone were weaned from mechanical ventilation earlier (12 vs. 16 days) and had a shorter length of ICU stay (18 vs. 24 days) than did those who received placebo. Three patients (4%) in the hydrocortisone group developed acute respiratory distress syndrome vs. 11 (14%) in the placebo group.

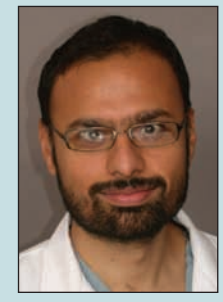
The two groups did not differ with respect to mortality, rate of other infections, number of organ failures, or duration of vasopressor support.

Both these beneficial effects and the safety of hydrocortisone therapy must be confirmed in future studies of ICU patients, particularly in those with traumatic brain injury, Dr. Roquilly and his associates said.

This study was sponsored by the University of Nantes. The French Ministry of Health provided additional support. No financial conflicts of interest were reported. ■

COMMENTARY

Dr. Nirupam Singh, FCCP, comments: Although the reduction in pneumonia rates is quite striking in this very well done French HYPOLYTE study, the much larger CRASH trial (10,000 patients), which used methylprednisone infusion, showed worse mortality. The HYPOLYTE authors reported only 28-day mortality.



As we have seen over the last decade, steroid use in the ICU has not panned out in either ARDS or sepsis when subjects were followed for longer than 28 days in more rigorous trials.

Very high rates of pneumonia attributed to the inflammatory response have been reported in trauma patients. However, the CRASH study had a pneumonia rate of 13%. It is surprising that the placebo group still had a 50% pneumonia rate in the era of greater scrutiny on cutting infection rates and implementation of various "bundles."

Bottom line: Results in this study are encouraging, but more data are definitely needed before steroids become the norm in trauma patients or practice is changed.

Dalteparin Not Better Than Heparin for DVT Prevention

BY MARY ANN MOON
Elsevier Global Medical News

The low-molecular-weight heparin dalteparin was found to be no better than unfractionated heparin in preventing proximal leg deep vein thrombosis among critically ill adults, according to an an international study.

Rates of venous thrombosis, venous thromboembolism, major bleeding, and death also were similar with the two agents. Although dalteparin was associated with significantly fewer pulmonary emboli and significantly less heparin-induced thrombocytopenia, these were not primary outcomes, and "caution is warranted in making inferences about nominally significant findings in secondary outcomes," said Dr. Deborah Cook and her coinvestigators in the Prophylaxis for Thromboembolism in Critical Care Trial (PROTECT). The study was published online simultaneously with its presentation at the International Symposium on Intensive Care and Emergency Medicine in Brussels.

VITALS

Major Finding: Among critically ill adults, proximal leg DVT developed in 5.1% of patients given dalteparin and 5.8% of those taking unfractionated heparin, a nonsignificant difference.

Data Source: An international blinded, randomized clinical trial involving 3,746 adults treated in 67 ICUs.

Disclosures: The PROTECT study was funded by the Canadian Institutes of Health Research, the Australian and New Zealand College of Anesthetists Research Foundation, and the Heart and Stroke Foundation of Canada. Study drugs were provided by Pfizer and Eisai. The investigators reported ties to numerous industry sources.

The study was done because two previous randomized trials comparing the two types of heparin were inconclusive. PROTECT was conducted in 67 ICUs within academic or community hospitals in Australia, Brazil, Canada, Saudi Arabia, the United Kingdom, and the United States. A total of 3,746 patients were randomly assigned in equal numbers to receive either dalteparin or unfractionated heparin to prevent thromboembolism.

Approximately three-fourths of the study subjects were medical patients and the remainder were surgical patients. Ninety percent required mechanical ventilation and 45% required vasopressors.

"Throughout the trial, the rates of cointerventions with drugs or devices that influence bleeding or thrombotic risk were similar in the two groups," noted Dr. Cook of the departments of medicine and clinical epidemiology and biostatistics at McMaster University, Hamilton, Ont., and her colleagues.

Twice a week until discharge, the study subjects underwent ultrasonography of the proximal venous system in the leg at 1-cm intervals to detect deep vein thrombosis (DVT). Compressibility was documented at the common femoral, proximal, middle, and distal superficial femoral and popliteal veins, and at the venous trifurcation.

Even though screening compression ultrasonography has limitations in this regard, it was chosen because "classic signs and symptoms of DVT do not develop in comatose, recumbent, critically ill patients." Moreover, it is safe, noninvasive, readily available, and recommended for such research, the investigators said.

The median duration of the use of both drugs was 7 days.

The primary end point – incident proximal leg DVT – developed in 96 (5.1%) of the patients receiving dalteparin, compared with 109 (5.8%) of those receiving unfractionated heparin, a nonsignificant difference.

However, "the confidence interval around the hazard ratio for the primary end point was fairly wide, so it did not exclude either a 32% benefit or a 23% harm associated with dalteparin, as compared with unfractionated heparin. Thus, the result for the primary outcome was not clinically directive," Dr. Cook and her associates said (N. Engl. J. Med. 2011 March 22 [doi:10.1056/NEJMoa1014475]).

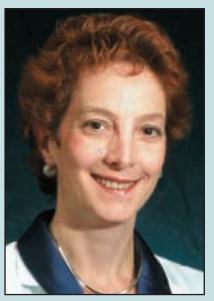
The rates of venous thrombosis, venous thromboembolism, major bleeding, and death also were similar between the two groups.

Patients in the dalteparin group had significantly fewer pulmonary emboli (1.3% vs. 2.3% of patients) and significantly less heparin-induced thrombocytopenia (0.3% vs. 0.6% of patients), but these outcomes must be interpreted with caution, given the small numbers, the researchers said.

These study findings were consistent in further adjusted analyses of the data, as well as in sensitivity analyses and a per-protocol analysis.

"Our results might have been different if the study enrollment had been larger or if we had used different drugs or doses," they noted. ■

COMMENTARY



Dr. Jeana O'Brien, FCCP, comments: The PROTECT study was designed to provide information regarding the benefit of unfractionated heparin vs. a specific LMWH (dalteparin) in critically ill patients. Despite literature regarding the significant incidence of DVT in the critically ill and need for preventive therapy, and support for the use of LMWH for DVT prevention in trauma and orthopedic patients, there is no consensus regarding the best option in medical ICU patients. The 8th edition of the ACCP Antithrombotic and Thrombolytic Guidelines suggests use of either LMWH or LDUH (low-dose unfractionated heparin) in this population. Fortunately for the patients, the numbers of events were small in both groups, and PROTECT does not allow conclusive support for use of dalteparin over unfractionated heparin, supporting the need for subsequent, larger trials.

ECMO's Value for Severe Hypoxic Lung Failure Questioned

BY MITCHEL L. ZOLER
Elsevier Global Medical News

LAS VEGAS – The evidence supporting use of extracorporeal membrane oxygenation for treating adult patients with severe hypoxic lung failure remains uncompelling, according to Dr. Alan H. Morris, FCCP.

He particularly advised against widespread use of extracorporeal membrane oxygenation (ECMO) in patients who have severe acute respiratory distress syndrome secondary to H1N1 influenza infection, as there is also no evidence that H1N1 patients treated with ECMO had better outcomes than those treated with standard ventilation support.

"We need results from a credible randomized controlled trial to define the conditions surrounding ECMO, before ECMO becomes a routine therapy option," said Dr. Morris, a pulmonologist and professor of medicine at the University of Utah and Intermountain Health Medical Center in Salt Lake City.

"There are indications and applications of extracorporeal support that are straightforward," such as when it is used intraoperatively, he said. But for patients with severe hypoxic lung failure, "I do not see compelling evidence that extracorporeal support is followed by more favorable outcomes than other approaches that are used," he said in an interview. "The evidence from the H1N1 novel influenza epidemic indicates to me that survival appears to be roughly the same with or without extracorporeal support," he added. "We do not offer ECMO as treatment for adult patients with severe hypoxic lung failure in my hospital."

The only two studies that examined the efficacy of ECMO in rigorously controlled clinical trials both failed to show that ECMO improved patient survival, he noted (JAMA 1979;242:2193-6; Am. J. Respir. Crit. Care Med. 1994;149:295-305). More recent results from a British multicenter randomized trial with 180 adults with severe respiratory failure claimed to show evidence that patient survival with ECMO surpassed survival with usual care (Lancet 2009;374:1351-63). But the newer study had the flaw of failing to define the usual care received by the control patients. In addition, the control patients were distributed to many centers, while all the ECMO patients received their treatment at one center, Dr. Morris said. The conventional ventilation that control patients received could be whatever their attending intensivist thought appropriate. "How does a clinician know which patients will benefit [from ECMO] without knowing what was conventional treatment?" he said.

To assess the impact of ECMO in patients with acute respiratory distress secondary to H1N1 infection, Dr. Morris summarized data reported on 150 patients in a University of Michigan registry; 14 patients seen in Salt Lake County, Utah, and reported last year in a paper at the American Thoracic Society; a series of 68 patients in Australia and New Zealand (JAMA 2009;302:1888-95); and 896 U.S. patients entered into a registry of the National Heart, Lung, and Blood Institute during 2009-2010. These data showed a consistent pattern of no improved survival with ECMO treatment in H1N1 patients, compared with H1N1 patients who did not receive ECMO, Dr. Morris said at the annual meeting of the National Association for Medical Direction of Respiratory Care.

A well-designed study to compare modern ECMO with other ventilation support methods would be a challenge, Dr. Morris said. A major problem is that the physicians "who have ECMO skills are convinced of its efficacy. Those who do ECMO don't believe that better testing is needed," he said.

Dr. Morris had no relevant financial disclosures. ■

COMMENTARY

Dr. Marcos Restrepo, FCCP, comments: This article describes a hot topic in critical care medicine regarding the value of ECMO to treat patients with severe hypoxic respiratory failure. This is a conservative opinion on the limited data to support the widespread use of ECMO. Further well-designed, randomized, controlled trials are needed to prove this hypothesis.

Revised Lung Allocation System Reduced Wait List

BY MITCHEL L. ZOLER
Elsevier Global Medical News

LAS VEGAS – The 2005 revision of the lung allocation system for U.S. lung transplants succeeded, resulting in fewer patients dying while on the lung waiting list, Dr. Robert M. Kotloff, FCCP, said at the annual meeting of the National Association for Medical Direction of Respiratory Care.

Reduced deaths in wait-listed patients "was the major goal" of the revision, "so the LAS [lung allocation system] worked," said Dr. Kotloff, professor of medicine and chief of the section of advanced lung disease and lung transplantation at the University of Pennsylvania in Philadelphia.

The new LAS also triggered other changes in the pattern of U.S. lung transplantations during the subsequent 5 years, some of which took several years to become apparent.

The revised system for allocation of donor lungs shifted the weight of the different pulmonary diseases that lead to lung transplantation, reducing the priority of chronic obstructive pulmonary disease (COPD) and boosting the importance of idiopathic pulmonary fibrosis (IPF). As recently as a decade ago, 45% of U.S. lung transplantations were done in patients with COPD and 20% in those with IPF. Although the gap between the two had narrowed considerably by 2005, that year COPD still remained the leading indication. But by 2007, IPF inched ahead of COPD, and today IPF is the leading reason why U.S. patients receive a lung transplant, Dr. Kotloff said.

"IPF is a no-brainer for listing," with a median survival of 3-4 years, and with half of IPF deaths occurring after a sudden patient decline, he said. Although some patients have an indolent form of IPF, "what's unsettling is that half of IPF deaths are sudden and unpredictable, occurring in patients who recently had stable or mild disease. We have all had IPF patients who were told they weren't sick enough to list and to return in 6 months – who then show up in the ICU on a ventilator, a missed opportunity" for transplantation. IPF patients now undergo a thorough evaluation for transplantation so that if they suddenly wind up in the ICU, it's easier to get them a transplant quickly.

Patients who receive a lung transplant have a median 5-year survival rate of 50%, which means that patients with a disease that has a similar or better prognosis are not good candidates. The poorer average survival rate of IPF patients helps explain why they are good transplant candidates.

The U.S. Department of Health and Human Services mandated a 2005 revision of the allocation systems for all organs based on medical urgency rather than time on the waiting list, a system biased against patients with more aggressive disease such as IPF. The LAS scoring formula put in place by the Organ Procurement and Transplantation Network took into account both the urgency of a patient's need for a lung transplant and the patient's likelihood of survival following transplantation (Chest 2007;132:1954-61). Two patient features carry the most weight in the formula: the patient's underlying disease, and whether the patient requires mechanical ventilation. Today, about the only way for a patient to have a really high LAS score of 80 or greater is to be on a ventilator with high-flow oxygen.

COMMENTARY

Dr. Joseph B. Barney, FCCP, comments: This short review of the LAS scoring system and the changes it has made in transplantation over the last 6 years is a good update for pulmonologists and thoracic surgeons.

The 2005 LAS revision led to a dramatic shortening of the U.S. waiting list for lungs – from more than 2,000 patients before 2005 to roughly 1,000 patients today – largely because it deemphasized time on the list and made "time banking" unnecessary. Time banking had been a practice by which potential lung transplant candidates without an immediate need got listed in case they needed a transplant in the future. If they did eventually need a transplant, they had accumulated time on the list, which boosted their chances of getting the transplant more quickly. If they eventually got a call for a transplant but still did not immediately need it, they could withdraw from accepting that organ but still retain their relatively high priority on the list, Dr. Kotloff explained.

With the new allocation formula, patients are simply kept off the list until their transplant need becomes clear. The downside is that many patients with potentially severe and unstable lung disease move from referral to listing to transplantation in just a few weeks – so rapidly that they do not have time to receive adequate counseling about the consequences and possible drawbacks of lung transplantation, Dr. Kotloff said.

Dr. Kotloff had no disclosures. ■

observed in an additional 22 patients 12 to 17 years of age who were treated with DULERA in another clinical trial. The safety and efficacy of DULERA have not been established in children less than 12 years of age.

Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in growth velocity in pediatric patients. In these studies, the mean reduction in growth velocity was approximately 1 cm per year (range 0.3 to 1.8 per year) and appears to depend upon dose and duration of exposure. This effect was observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for "catch up" growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied.

The growth of children and adolescents receiving orally inhaled corticosteroids, including DULERA, should be monitored routinely (e.g., via stadiometry). If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect should be considered. The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of orally inhaled corticosteroids, including DULERA, each patient should be titrated to his/her lowest effective dose *[see Dosage and Administration (2.2)]*.

8.5 Geriatric Use

A total of 77 patients 65 years of age and older (of which 11 were 75 years and older) have been treated with DULERA in 3 clinical trials up to 52 weeks in duration. Similar efficacy and safety results were observed in an additional 28 patients 65 years of age and older who were treated with DULERA in another clinical trial. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As with other products containing $beta_2$-agonists, special caution should be observed when using DULERA in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by $beta_2$-agonists. Based on available data for DULERA or its active components, no adjustment of dosage of DULERA in geriatric patients is warranted.

8.6 Hepatic Impairment

Concentrations of mometasone furoate appear to increase with severity of hepatic impairment *[see Clinical Pharmacology (12.3)]*.

10.1 Signs and Symptoms

DULERA: DULERA contains both mometasone furoate and formoterol fumarate; therefore, the risks associated with overdosage for the individual components described below apply to DULERA.

Mometasone Furoate: Chronic overdosage may result in signs/symptoms of hypercorticism *[see Warnings and Precautions (5.7)]*. Single oral doses up to 8000 mcg of mometasone furoate have been studied on human volunteers with no adverse reactions reported.

Formoterol Fumarate: The expected signs and symptoms with overdosage of formoterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the following signs and symptoms: angina, hypertension or hypotension, tachycardia, with rates up to 200 beats/min., arrhythmias, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, and insomnia. Metabolic acidosis may also occur. Cardiac arrest and even death may be associated with an overdose of formoterol.

The minimum acute lethal inhalation dose of formoterol fumarate in rats is 156 mg/kg (approximately 63,000 times the MRHD on a mcg/m^2 basis). The median lethal oral doses in Chinese hamsters, rats, and mice provide even higher multiples of the MRHD.

10.2 Treatment

DULERA: Treatment of overdosage consists of discontinuation of DULERA together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of DULERA. Cardiac monitoring is recommended in cases of overdosage.

Manufactured by 3M Health Care Ltd.,
Loughborough, United Kingdom.
Manufactured for Schering Corporation, a subsidiary of

MERCK & CO., INC.
Whitehouse Station, NJ 08889 USA.

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Ginseng Cuts Respiratory Infections in Elderly

Leukemia patients taking the ginseng supplement did not benefit significantly.

BY ERIK L. GOLDMAN
Elsevier Global Medical News

NEW YORK – A standardized extract of American ginseng (*Panax quinquefolium*) has been shown to be safe and effective in reducing the incidence and severity of acute respiratory infections among both community-dwelling and institutionalized elderly people.

However, the same product was not effective in decreasing respiratory infections among people with chronic lymphocytic leukemia (CLL), a condition that leaves patients particularly vulnerable to influenza and other acute respiratory infections (ARIs), reported Dr. Edward G. Shaw at an International Conference Sponsored by the Society for Integrative Oncology.

The promising findings from three studies among otherwise healthy elderly individuals led to the hope that this particular extract, known as CVT-E002 and marketed as an over-the-counter product called COLD-FX, might be similarly effective in patients with CLL, said Dr. Shaw of the Comprehensive Cancer Center, Wake Forest University, Winston-Salem, N.C.

CLL is the most common adult form of leukemia, affecting roughly 20/100,000 Americans. Because of the associated anemia, thrombocytopenia, and compromised immune system function, CLL survivors are at substantially increased risk of infections, especially respiratory infections. Common drug therapies like chlorambucil and fluorouracil increase this risk.

"There is a pressing need for effective, relatively low-cost interventions to reduce infection risk in CLL patients," Dr. Shaw said.

Panax ginseng is a reasonable botanical candidate for that job. Although it is indigenous to the United States and Canada, it is commonly used in traditional Chinese medicine and other Asian healing traditions. It is widely promoted as an immune system booster, and a number of preclinical and clinical studies support this claim.

The CVT-E002 extract, marketed by Afexa Life Sciences, is standardized to provide consistent doses of immunologically active compounds poly-furanosyl-pyranosyl-saccharides, which enhance natural killer cell activity, Dr. Shaw said. It is the only American ginseng extract that has been granted investigational new drug clearance by the U.S. Food and Drug Administration.

In 2004, Dr. Janet McElhaney of Eastern Virginia Medical School, Norfolk, published data from two studies of 89 and 109 people (mean age, 81 and 83.5 years, respectively) in nursing home and assisted living settings. The subjects were randomized to the ginseng extract (200 mg twice daily) or to placebo. The first trial lasted 8 weeks, and the second ran for 12. In both study cohorts, upward of 90% of the subjects had been vaccinated against influenza infections.

An episode of ARI was defined as two or more concurrent respiratory symptoms or one respiratory plus one constitutional symptom. Infectious diagnoses were confirmed by culture and serology.

Using an intent-to-treat analysis, Dr. McElhaney and her colleagues pooled the data from the two distinct trials. They found that lab-confirmed influenza was more common among the placebo group (seven cases in 101 subjects), compared with the ginseng-treated group (one case in 97 subjects). Incidence of influenza and respiratory syncytial virus infections combined was also higher in the placebo vs. the ginseng group (nine cases vs. one case). These differences were statistically significant (J. Am. Geriatr. Soc. 2004;52:13-9).

Interestingly, the investigators found no difference between the active treatment and placebo groups in terms of subjective reporting of ARI symptoms; roughly one-third of the people in each group reported ARI episodes, though the incidence of actual lab-confirmed infections was far lower.

Approximately 90% of the subjects in both groups reported adverse effects, the most common being gastrointestinal related. A total of 8% of the placebo group and 4% of the ginseng group required hospitalization, but none of these admissions was related to the study medications.

In 2006, Dr. McElhaney – now at the Center for Immunotherapy of Cancer and Infectious Diseases, University of Connecticut, Farmington – published a trial of the same COLD-FX ginseng formula vs. placebo in a cohort of 43 community-dwelling adults aged 65 years and older. As in the previous trial, the ginseng dose was two 200-mg extract capsules daily, for a period of 4 months. After the first month of the trial, all subjects in both groups were immunized against influenza.

The investigators observed a significant reduction in episodes of ARI during November and December, the closing months of the trial. Of the placebo-treated group, 62% had an ARI episode, compared with 32% of those taking the CV-E002 extract. Duration of symptoms was also considerably longer in the placebo group (12.6 days vs. 5.6 days). Lab confirmation of infection was not done in this study (J. Altern. Complement. Med. 2006;12:153-7).

OF THE PLACEBO-TREATED GROUP, 62% HAD AN ACUTE RESPIRATORY INFECTION, COMPARED WITH 32% OF THOSE TAKING THE GINSENG EXTRACT.

Adverse effects were few in both groups, and there was no significant difference between them. All of these studies were funded in part by CV Technologies, the company that manufactures the CVT-E002 extract.

These data, along with positive results from a Canadian study (CMAJ 2005; 173:1043-8), prompted the Wake Forest group to look at the potential of the ginseng extract to reduce infection risk in CLL patients.

A total of 293 untreated CLL patients were randomized to take COLD-FX, 200 mg twice daily, or matching placebo for 3 months. The patients were instructed to keep a daily record of ARI symptoms in written diaries and to rate their symptoms on a 0-3 scale of severity. Subjects also recorded activity limitations, episodes of fever, and antibiotic use.

The patients had a mean age in the mid-60s; 75% of the active treatment group and 78% of the placebo group had been vaccinated against influenza. The investigators excluded people with HIV, cirrhosis, cardiovascular disease, multiple sclerosis, other malignancies, and liver enzyme abnormalities. They also excluded people on immunomodulatory drugs, hematopoietic stem cell recipients, and those on corticosteroids, antibiotics, or warfarin.

Of all subjects, 53% had an ARI during the study period from January to March. On average, ARI days occurred at a rate of 0.1/patient-day. Put another way, 1 of every 10 days is an ARI day for these patients, Dr. Shaw explained. Since only about half of the subjects actually had ARIs, this means that for them 1 out of every 5 days is an ARI symptom day.

Overall, there were no major differences between the treatment and placebo groups in terms of the primary study end points. In the ginseng-treated group, 50% had at least one ARI episode, compared with 55% in the placebo group, but this difference was not statistically significant.

In terms of symptom duration, the ginseng group had a mean total of 8.9 ARI days vs. 6.9 days, but this difference was also deemed not statistically significant.

There were no differences in use of antibiotics or other secondary end points. While there was a trend toward lower incidence of moderate to severe ARIs in patients taking the ginseng supplement (31% vs. 39%), it did not reach significance.

In terms of adverse events, there were 13 "serious" episodes in the ginseng group versus 27 in the placebo group. Diarrhea, dizziness, hyperglycemia, and joint pain were among the most common reported adverse effects, but these were rare, and only 2 of the 40 episodes were considered "possibly related to the treatment."

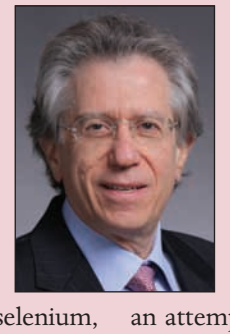
Both the ginseng-treated and placebo-treated groups showed a mean increase in total white blood cells, with the increase being slightly higher in the placebo group. However, both groups showed a decrease in absolute neutrophil counts. Peripheral blood CD4 cell counts decreased in the active treatment group but increased in the placebo group. None of these differences were statistically or clinically significant.

The study was funded by the National Cancer Institute and Afexa Life Sciences.

The researchers said they did not know why the ginseng extract failed to produce the expected reductions in ARI among these CLL patients, but suggested that it may be a dosing issue. "We went with the dose used in the previous studies of healthy elderly, non-cancer patients. It might not have been enough for CLL patients with impaired immune function." Dr. Shaw added that dose-escalation studies are in the works. ■

COMMENTARY

Dr. Stuart Garay, FCCP, comments: Although some herbal remedies can indeed be beneficial, others may not work or even be harmful. There are very few controlled studies regarding efficacy and safety of many of these substances. In the past decade, various alternative medicines have been promoted for preventing and/or mitigating respiratory infections including N-acetylcysteine, zinc, selenium, and American ginseng (*Panax quinquefolium*).



Previous research had suggested that the use of American ginseng reduced the incidence and severity of acute respiratory infections in elderly patients – both institutionalized and those living in the community. It is thought that Panax ginseng acts as an immunomodulator. Some studies suggest that Panax ginseng has various actions including increased immunoglobulin production, stimulation of macrophage responsiveness, increased phagocytosis, and activation of natural killer and CD8 cells, as well as promoting expression of IL-2 and interferon.

This study, as well as previous studies (J. Am. Geriatr. Soc. 2004;52: 13-9; J. Altern. Complement. Med. 2006;12: 153-7) looking at normal elderly patients, represent an attempt to scientifically analyze the effects of a specific herbal remedy. Until future studies are available, remember: *primum non nocere* (first, do no harm).

While herbs such as American ginseng are fairly safe, they have potential side effects and drug interactions (especially with warfarin and MAO inhibitors).

More studies like this one are needed – especially in patients with pulmonary diseases.

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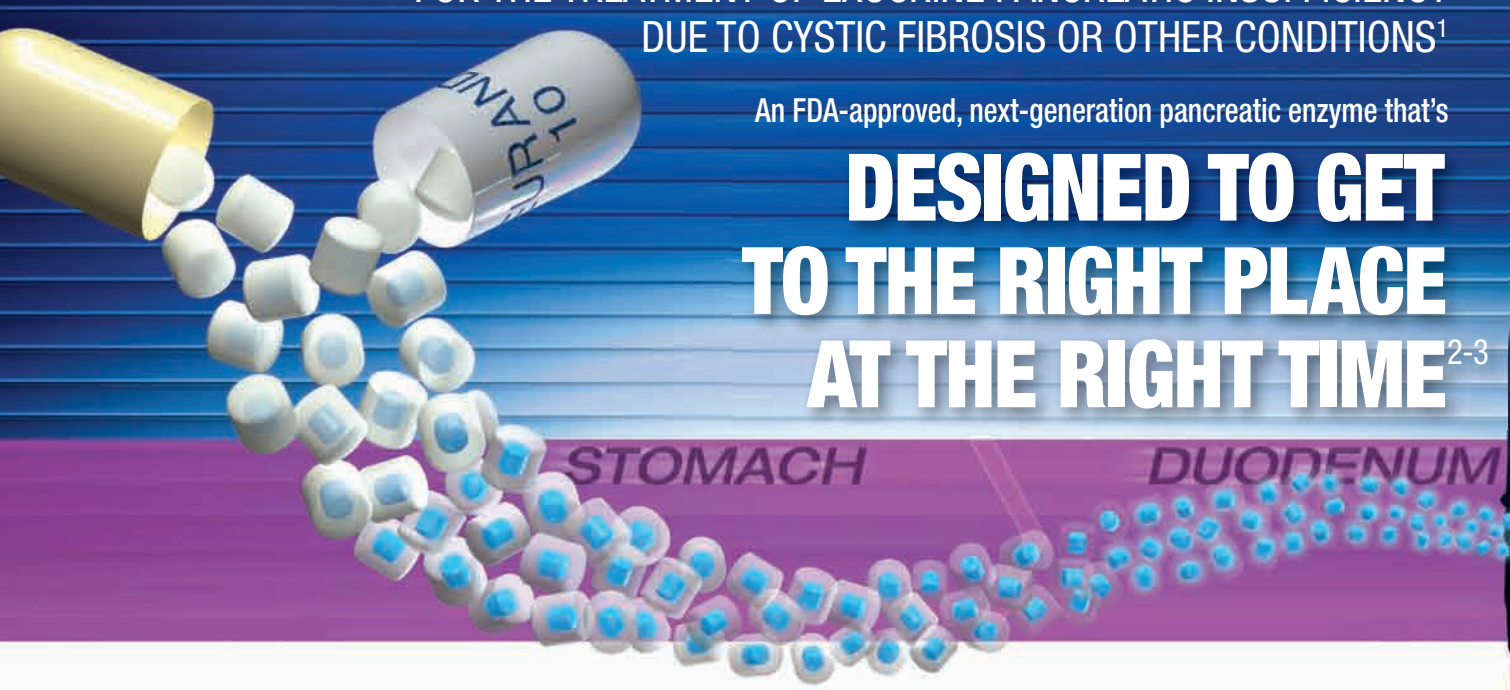

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- Results were achieved without the use of concomitant agents such as PPIs, H_2-antagonists, and motility agents[4]

...with improved symptom control, even when switched from a previous enzyme[4]

- 100% (N=19) of children with PI due to CF switched to ZENPEP from a previous unapproved pancreatic enzyme had improved or maintained their level of symptom control (secondary endpoint)[4]
  - In this open-label, uncontrolled trial of patients aged 1 to 6 years, parents/guardians reported that 47% of patients switched to ZENPEP had improved symptom control (n=9) and 53% maintained symptom control (n=10)[4]*
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Important Safety Information

- Fibrosing colonopathy is a rare serious adverse reaction associated with high-dose use of pancreatic enzyme replacement products and most commonly reported in pediatric patients with CF. Exercise caution when doses of ZENPEP exceed 2500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of body weight per day)
- Exercise caution when prescribing ZENPEP to patients with gout, renal impairment, or hyperuricemia and when administering pancrelipase to a patient with a known allergy to proteins of porcine origin
- To avoid irritation of oral mucosa or inactivation of enzymes, do not chew ZENPEP capsules or beads or retain in the mouth
- There is theoretical risk of viral transmission with all pancreatic enzyme products, including ZENPEP

Please read Brief Summary of Prescribing Information on adjacent page and provide Medication Guide to patients prescribed ZENPEP.

*Reports were subjective and recorded in a daily diary form.[4]

References: 1. ZENPEP [package insert]. Yardley, PA: Eurand Pharmaceuticals, Inc.; 2010. **2.** Data on file MED-0151, Eurand Pharmaceuticals, Inc., Yardley, PA. **3.** Data on file MED-0152, Eurand Pharmaceuticals, Inc., Yardley, PA. **4.** Wooldridge JL, Heubi JE, Amaro-Galvez R, et al. EUR-1008 pancreatic enzyme replacement is safe and effective in patients with cystic fibrosis and pancreatic insufficiency. *J Cyst Fibros*. 2009;8(6):405-417.

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Office-Based Aspirin Desensitization May Be Safe

VITALS

Major Finding: Fifteen patients with aspirin-exacerbated respiratory disease tolerated desensitization to aspirin in an outpatient setting.

Data Source: Retrospective chart review of patients desensitized to aspirin using a 1-day protocol in a clinic.

Disclosures: The investigators reported having no financial conflicts of interest.

BY SHERRY BOSCHERT
Elsevier Global Medical News

SAN FRANCISCO – A small, retrospective study suggests that patients with aspirin-exacerbated respiratory disease may be safely desensitized to aspirin in an office setting rather than in a hospital.

Each of 15 patients who underwent a 1-day aspirin desensitization protocol in a clinic completed the protocol and ingested a cumulative total of 568 mg of aspirin on average by the end of the day. Each was then able to tolerate taking aspirin up to 650 mg b.i.d., Richard S. Dunn and Dr. Richard W. Hendershot reported in a poster presentation at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

In-hospital aspirin desensitization for patients with aspirin-exacerbated respiratory disease typically takes 2-3 days, and some clinicians recommend doing it in an ICU, said Mr. Dunn, a fourth-year medical student at the University of Utah, Salt Lake City. Dr. Hendershot is an allergy and immunology specialist with Intermountain Healthcare in Salt Lake City.

The outpatient protocol took 8-9 hours. The cost to desensitize a patient averaged $2,678 in the outpatient clinic, compared with an average daily cost for ICU care of $13,347 reported in the literature.

Desensitization started with application of intranasal ketorolac three times over half-hour intervals. Patients then ingested 81 mg of aspirin and increased the dose by 81 mg every 2 hours to a final dose of 325 mg.

They were closely monitored during the desensitization. No complications were seen in 56% of patients. FEV_1 (forced expiratory volume in 1 second) decreased by more than 20% in 19% of patients; 13% of patients developed flushing, and dyspnea or urticaria was each seen in 6% of patients.

Approximately 21% of people with asthma and 40% of patients with asthma who are dependent on glucocorticoids have aspirin-exacerbated respiratory disease. These patients often present with asthma, chronic rhinosinusitis, and nasal polyps. If they ingest a cyclooxygenase-1 inhibitor, they develop asthma symptoms, rhinorrhea, periorbital edema, urticaria, pruritus, angioedema, anaphylaxis, or other symptoms.

The design of the desensitization protocol was borrowed from a similar protocol that was tested in a controlled study of 100 patients (Ann. Allergy Asthma Immunol. 2010;105:130-5).

A patient who could not afford desensitization in the hospital inspired the development of the outpatient protocol that was used in the study.

The results suggest that aspirin desensitization for the treatment of aspirin-exacerbated respiratory disease can be done safely and efficaciously in the outpatient setting in less time and with less cost, compared with inpatient treatment protocols, the investigators concluded. ■

COMMENTARY

Dr. Darcy Marciniuk, FCCP, comments: The outcomes from this work suggest that ASA desensitization can safely be undertaken in a supervised outpatient setting. Because complications still occur, close monitoring and skilled staff are required. However, the success of this pilot project implies that hospitalization may no longer be necessary for the vast majority of the patients who undergo aspirin desensitization.

Quality of Life in Asthma Improved Little Over a Decade

BY M. ALEXANDER OTTO
Elsevier Global Medical News

SAN FRANCISCO – Physicians don't always follow national asthma guidelines, and quality of life has improved only slightly for asthma patients since 1998, according to two studies.

We have not moved the pendulum very far despite of all the information and studies that have occurred over the last 12 to 13 years. [Doctors] know about the guidelines, but they don't incorporate them into practice. Three and a half years of writing guidelines didn't change a thing," said asthma specialist Dr. Stuart Stoloff, a clinical professor at the University of Nevada, Reno, and one of the experts who worked on the National Heart, Lung, and Blood Institute guidelines.

The problem is "patients have not received information about how good they should be able to feel. The other part of it is that clinicians who provide care for those patients are not aware of how well someone should feel with the disease," said Dr. Stoloff, an author on both studies, which were presented at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

The first study compared 1998 Asthma in America survey results from 2,509 pediatric and adult asthma patients with 2009 Asthma Insight and Management survey results from 2,500 pediatric and adult asthma patients, assessing disease burden and other issues. The findings: Asthma exacerbations sent about the same percentage of patients to the emergency department or hospital in 2009 as in 1998, while the 2009 patients missed only slightly less work or school due to asthma.

In 1998, 64% of adults said asthma limited their daily activities. In 2009, it was 55%. About 28% of patients owned peak-flow meters in 1998 and 35% had lung function testing in the previous year. In 2008, 35% owned a meter and 33% had their lungs tested within a year.

In the second study, 309 asthma specialists and general practitioners were surveyed. The findings reveal that what many consider to be adequate asthma control falls short of treatment goals in the NHLBI 2007 Guidelines for the Diagnosis and Management of Asthma.

About 96% of physicians surveyed knew about the NHLBI guidelines, but only 28% said that they "always" complied with them. The numbers were slightly higher for allergists and pulmonologists.

Half of physicians considered asthma well managed if patients had two urgent doctor visits per year. About a third considered both one ED visit and three to four exacerbations per year compatible with good management. One in five physicians thought patients who needed quick relief medication three times per week were well managed.

For adults with mild persistent asthma, only 67% of physicians overall preferred inhaled corticosteroid monotherapy as the first-line treatment, though the number was a bit higher for specialists. Only about half reported drawing up asthma action plans as recommended by the guidelines for most or all of their patients.

Dr. Stoloff said pay for performance is a solution. Physicians should be rewarded for good outcomes and compensated for patient education and other efforts to achieve good outcomes.

Accountable care organizations and patient-centered medical homes are moving in that direction, but "we need to accelerate the process," he said.

Asthma mortality has decreased in recent years because of better diagnosis and treatment, but Dr. Stoloff said the findings indicate that change is "not occurring fast enough."

Outcome benchmarks in pay-for-performance models should include "patients going to school, going to work, going to play" and "normal or near-normal lung function; not ending up in an emergency room or hospital; [and] not taking oral steroids," he said. ■

VITALS

Major Finding: Asthma exacerbations sent about as many patients to the hospital or emergency department in 2009 as they did in 1998; only 28% of physicians report "always" complying with asthma guidelines.

Data Source: In one study, patient survey results from 1998 were compared with patient survey results from 2009; in the second study, asthma specialists and general practitioners were surveyed and their responses were compared with NHLBI guidelines.

Disclosures: Dr. Stoloff is a consultant for AstraZeneca, Alcon, Merck, Novartis, Dey Pharma, GlaxoSmithKline, Boehringer-Ingelheim, Sepracor, and Teva Pharmaceuticals. The studies were funded by Merck.

COMMENTARY

Dr. Darcy Marciniuk, FCCP, comments: It is become apparent we need to raise physicians' expectations for their patients suffering from asthma – regular urgent care visits for poor control are unacceptable. It is also very clear we need to adhere more closely to clinical practice guidelines designed to optimize patient care. If we don't start doing it ourselves, someone else will do it for us!

Helping Patients With Flight Plans

Travel • *from page 1*

and issues specific to the immunocompromised, Dr. Millard said at a pediatric pulmonology seminar sponsored by the American College of Chest Physicians and the American Academy of Pediatrics.

Air travel for pulmonology patients can be difficult, Dr. Millard noted, because "the environment is very dangerous." The cabin is pressurized, alveolar partial pressure falls with increasing altitude, and the partial pressure of oxygen is inversely proportional to altitude. Because the Joint Aviation Authorities stipulated that mean cabin pressure match an altitude of 8,000 feet, "this means they want us to all have an oxygen saturation of about 90%."

Supplemental oxygen during air travel can help patients, but identification of appropriate candidates varies. Guidelines from the American Thoracic Society and British Thoracic Society (Thorax 2002; 57:289-304) recommend that patients with chronic lung disease be able to maintain an arterial oxygen tension greater than 50 mm Hg or 6.6 kilopascals (kPa), said Dr. Millard. However, because they tend to be younger than COPD (chronic obstructive pulmonary disease) patients and generally have no increased cardiovascular risk, use of such a cutoff value could be an oversimplification for patients with cystic fibrosis, said Dr. Millard, a pediatric pulmonologist at Helen DeVos Children's Hospital in Grand Rapids, Mich.

Hypoxia during flight is a major concern. Consider whether your patient will be able to sustain hyperventilation that is spurred by hypoxia while on the airplane. Significant bronchospasm, for example, could impede prolonged hyperventilation, Dr. Millard said.

Consider a hypoxia inhalation test in advance of travel. This test requires that patients breathe a hypoxic mixture of 15% oxygen with nitrogen for 20 minutes to predict their reaction to hypoxia at 8,000 feet. Supplemental oxygen is recommended if their arterial oxygen tension drops below 50-55 mm Hg or 6.6-7.4 kPa.

"The hypoxia inhalation test is found to be safe," Dr. Millard said. Applicability outside the clinic setting is a concern, however: "The problem is, they are sitting. This may not fully represent the physical stress and environmental variability of air travel," including Transportation Security Administration screening and walking long distances. For this reason, some experts advise also screening patients with a walk test prior to their trip, she said.

Patients who require supplemental oxygen are permitted to use their own approved portable oxygen concentrator (POC) on all airlines that operate in the United States. POCs weigh 8-10 pounds and batteries last an average of about 4 hours, Dr. Millard said. Also, some POCs are pulse generated, meaning the patient must be able to inspire strongly enough to get oxygen.

Advise your patients or their families to check in advance if their airline requires approval from a physician for POC use, Dr. Millard said. "I had a patient who gave me 48 hours notice that they were going to fly. I had to fill out a form ahead of time for the airline."

Pulmonology patients also may request a travel letter, "which is especially important if they are going through customs," Dr. Millard said. Include their insurance information, your contact information, the telephone number for the clinic, and a list of medications (and approximate quantities required).

Airborne infection risk is another major concern. Most commercial aircraft recirculate 50% of the air delivered to the passenger cabin, Dr. Millard said. Ideally, the aircraft features HEPA (high-efficiency particulate air) filters, although the U.S. Federal Aviation Authority (FAA) and the U.K. Civil Aviation Authority do not mandate this level of filtration.

COMMENTARY

Dr. Jeana O'Brien, FCCP, comments: Many patients with lung disease look to their pulmonologist to provide guidance regarding safety and preparedness for air travel. Given the increasing desire for travel in our patient population, this article would seem useful to keep on hand.

Dr. Millard cited a study that supports transmission of H1N1 influenza during flight (Epidemiol. Health 2010;32: e2010006). Officials at the Korea Centers for Disease Control and Prevention determined that an infected woman who flew from Los Angeles to Seoul in 2009 infected other passengers. The study includes a seating map of the Boeing 747 that shows where she and other passengers who got sick were seated.

"People are trying to figure this out to make [air travel] safer," Dr. Millard said. For example, one set of researchers assessed the ability of commercially available biosensors to detect airborne pathogens on airplanes (PLoS One 2011; 6:e14520). With the current technology, however, only steady-state bacteria concentrations were detected in cases in which at least seven infected passengers either coughed 20 times per hour or sneezed 4 times an hour. And no sensor in the study detected airborne viruses well. Sensors with improved sensitivity and/or the screening of individual patients for respiratory illnesses prior to boarding might reduce the infection risk, Dr. Millard said.

For a list of POC devices that have been approved by the FAA, visit www.faa.gov/about/initiatives/cabin_safety/portable_oxygen. For additional guidance from the TSA on traveling with supplemental oxygen, you can refer patients to www.tsa.gov/travelers/airtravel/specialneeds/editorial_1374.shtm.

Dr. Millard had no disclosures. ■

Testing Alters Treatment Plan

EGFR • *from page 1*

demonstrating that mutations in two regions of EGFR gene appear to predict tumor response to chemotherapy in general, and to TKIs specifically.

Among the research priorities identified by ASCO, Dr. Keedy noted the trials that are designed to discern whether first-line treatment with a TKI in EGFR mutation–negative patients delays chemotherapy or affects outcome; whether chemotherapy prior to TKI treatment in EGFR mutation–positive patients affects outcome; and whether there are clinically significant differences between erlotinib (Tarceva) and gefitinib (Iressa) among EGFR mutation–positive patients.

The last question is of particular interest, because gefitinib is not Food and Drug Association approved outside a special program in the United States, whereas erlotinib is currently approved as second-line therapy, she said.

Dr. Ettinger, chair of the NCCN's NSCLC guideline panel and professor of oncology at Johns Hopkins University in Baltimore, cited findings from the landmark IPASS (Iressa Pan-Asia Study) investigation that compared progression-free and overall survival in 1,217 East Asian patients with advanced NSCLC that was treated with the gefitinib or standard carboplatin and paclitaxel chemotherapy.

IPASS demonstrated that EGFR mutation strongly predicted a lower risk of progression on gefitinib vs. chemotherapy (hazard ratio, 0.48), whereas wild-type EGFR predicted a higher risk of progression on gefitinib relative to chemotherapy (HR, 2.85) (N. Engl. J. Med. 2009;361:947-57).

Similarly, in a pooled analysis of clinical outcomes of NSCLC patients who were treated with erlotinib, EGFR mutations were associated with a median progression-free survival of 13.2 vs. 5.9 months (J. Cell. Mol. Med. 2010;14: 51-69). Neither study demonstrated a difference in overall survival among treated patients with and without EGFR mutations, Dr. Ettinger said.

The updated NCCN guidelines also state that the sequencing of KRAS (a G protein involved in the EGFR-related signal transmission) could be useful for the selection of patients as candidates for TKI therapy. The KRAS gene can harbor oncogenic mutations that may render a tumor resistant to EGFR-targeting agents, Dr. Ettinger explained, noting that studies have shown that a KRAS mutation in patients with NSCLC "confers a high level of resistance" to TKIs.

Although the data – which primarily come from retrospective reviews with small sample sizes – are insufficient to make a determination about an association between KRAS mutation status and survival, he said, they are sufficient to warrant a category 2A recommendation for sequencing, as well as a recommendation that patients with a known KRAS mutation should undergo first-line therapy with an agent other than a TKI.

Individuals who test negative for EGFR and KRAS should also be screened for a mutation of the anaplastic lymphoma kinase (ALK) fusion gene, Dr. Ettinger said. "Patients who screen positive may not benefit from EGFR TKIs, but they may be good candidates for an ALK-targeted therapy," he said, noting that the investigational ALK-targeting drug crizotinib, in particular, has demonstrated positive results in early studies of NSCLC patients with echinoderm microtubule-associated proteinlike 4 (EML4)-ALK translocations (N. Engl. J. Med. 2010;363:1693-703).

With respect to first-line systemic therapy, patients with adenocarcinoma, large cell carcinoma, or NSCLC "not otherwise specified" who have an Eastern Cooperative Oncology Group/World Health Organization performance status grade of 0-4 and who test positive for the EGFR mutation prior to first-line therapy should be treated with erlotinib, according to the NCCN guidelines. Alternatively, the guidelines state that gefitinib can be used in place of erlotinib "in areas of the world where it is available."

For patients in whom the EGFR mutation is discovered during chemotherapy, the guidelines recommend either adding erlotinib to the current chemotherapy protocol or switching to erlotinib as maintenance treatment.

For patients whose EGFR status is negative or unknown, even in the presence of clinical characteristics that might be suggestive of a mutation (for example, female, nonsmoker, Asian race), conventional chemotherapy is recommended, Dr. Ettinger said.

In an editorial that accompanied ASCO's PCO announcement, Dr. Paul A. Bunn Jr. and Dr. Robert C. Doebele of the University of Colorado Cancer Center in Aurora wrote that the growing clinical importance of molecularly defined subgroups of adenocarcinoma signals a "new era of personalized medicine for patients with advanced lung cancer, in which it will be imperative to match the specific mutations of a patient's tumor with a specific therapy."

The implementation of routine, simultaneous testing of multiple markers will likely be conducted on all patients prior to treatment initiation, regardless of clinical features, they added.

Dr. Ettinger has consultancy agreements with several pharmaceutical companies. Dr. Keedy receives commercial research support from Ariad Pharmaceuticals, Ziopharm Oncology, and Amgen Oncology Therapeutics. Dr. Bunn has a consultant or advisory role with several pharmaceutical companies. Dr. Doebele disclosed research funding from Lilly, ImClone Systems, and Pfizer. ■

COMMENTARY

Dr. W. Michael Alberts, FCCP, comments: The promise of personalized cancer treatment is becoming a reality. The choice of chemotherapy agents driven by routine testing for EGFR mutations in patients with adenocarcinoma of the lung, as advocated by ASCO and the NCCN, is but one example. Look for many more in the near future.

Other Updates From NCCN

The updated NCCN guidelines take a conservative stance on the National Lung Screening Trial finding that screening with low-dose helical CT was associated with a 20% reduction in lung cancer deaths vs. screening with standard chest x-ray.

Despite this positive finding, "the NCCN panel does not recommend the routine use of screening CT as a standard clinical practice," Dr. Ettinger said; more conclusive data from ongoing national trials are needed to define the associated risks and benefits.

"High-risk patients should participate in a clinical trial evaluating CT screening or go to a center of excellence to discuss the potential risks and benefits of a screening CT," he said.

Other notable updates include:

► The addition of EBUS (endobronchial ultrasound) as a work-up recommendation.

► The recommendation that bevacizumab (Avastin) and chemotherapy or chemotherapy alone is indicated in performance status 0-1 patients with advanced or recurrent NSCLC, and that bevacizumab should be given until disease progression.

► The recommendation against systemic chemotherapy in performance status 3-4 NSCLC patients.

► The guidance that chemoradiation is better than chemotherapy alone in locally advanced NSCLC, and that concurrent chemoradiation is better than sequential chemoradiation.

► The addition of denosumab (Xgeva) for patients with bone metastases.

► The recommendation favoring cisplatin/pemetrexed (Alimta) vs. cisplatin/gemcitabine (Gemzar) in patients with nonsquamous histology.

► The recommendation against adding a third cytotoxic drug, with the exception of bevacizumab or cetuximab (Erbitux), in treatment-naive performance status 0-1 NSCLC patients.

► The guidance that cisplatin-based combinations are better than best supportive care in incurable disease.

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*

Discover a NEW IV Cephalosporin for

COMMUNITY-ACQUIRED BACTERIAL PNEUMONIA

CABP AND ABSSSI

ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS

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.

NEW
Teflaro™
(ceftaroline fosamil) for injection
600 mg • 400 mg

Introducing TEFLARO™

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*.
- 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*.
- 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 cephalosporins, 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.

Broad-spectrum coverage for treating CABP and ABSSSI

Bactericidal Activity Against a Broad Spectrum of Gram-positive and Gram-negative Pathogens, Including *S. pneumoniae* in CABP and MRSA in ABSSSI[1]

Proven efficacy in 2 common infections
in patients admitted to the hospital[1,2]

CABP | **ABSSSI**

- Convenient q12h dosing in CABP and ABSSSI[1]
  - 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.

NEW
Teflaro™
(ceftaroline fosamil) for injection
600 mg • 400 mg

Demonstrated efficacy in CABP

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 Study Populations		
Day 4 Population (mITT)*		A microbiological intent-to-treat population (mITT population) containing only subjects with a confirmed bacterial pathogen at baseline.
Test of Cure (TOC) Populations†		
MITT	Modified Intent-to-treat	All randomized subjects who received any amount of study drug.
MITTE	Modified Intent-to-treat Efficacy	All subjects in the MITT population who were in PORT Risk Class III or IV at baseline.
CE	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.
ME	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).

* To evaluate the treatment effect of ceftaroline, an analysis was conducted in CABP patients for whom the treatment effect of antibacterials 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

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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 CABP that is proven or strongly suspected to be caused by susceptible bacteria.

IMPORTANT SAFETY INFORMATION

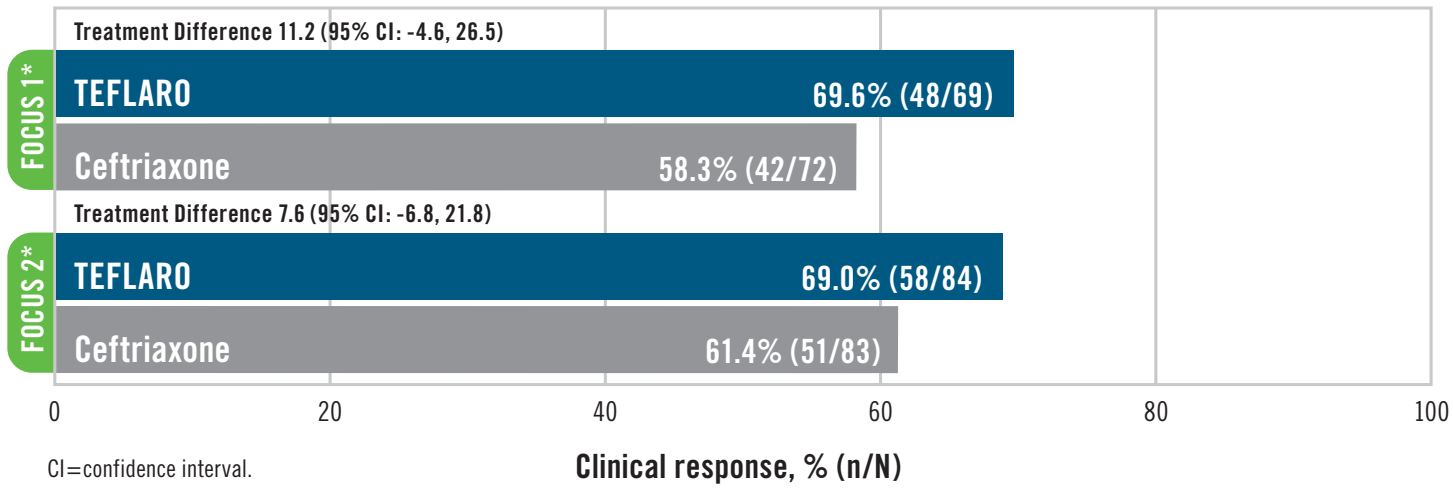
Adverse Reactions

- 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.

CABP

TEFLARO Demonstrated Clinical Response at Day 4 (mITT) in Community-Acquired Bacterial Pneumonia[1]

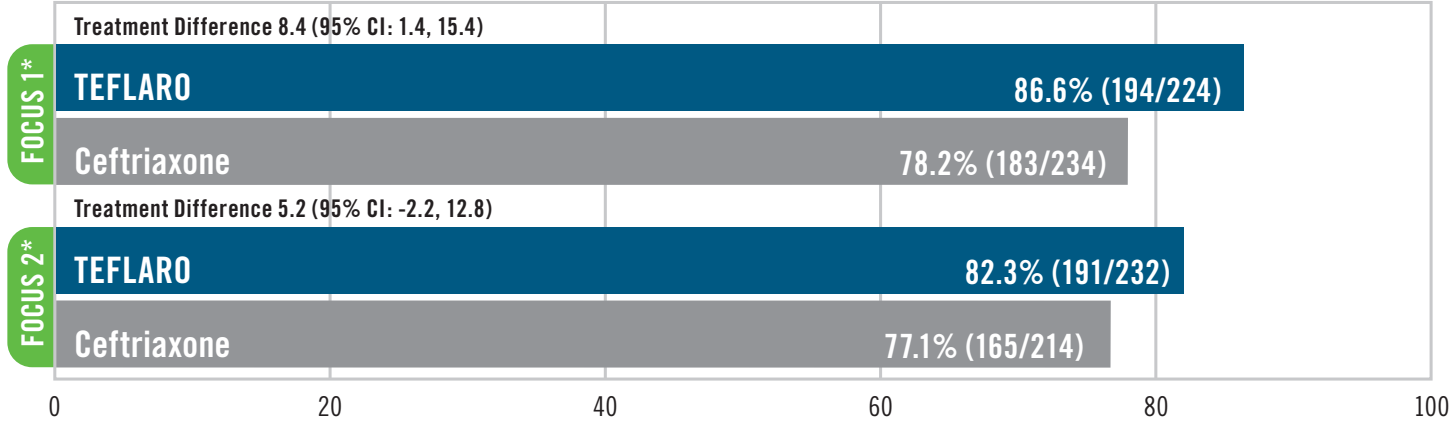


CI=confidence interval.

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

CABP

TEFLARO Demonstrated Efficacy at TOC† (CE) in Community-Acquired Bacterial Pneumonia[1]



CI=confidence interval.

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=Ce**f**tar**o**line **C**ommunity-Acquired Pne**u**monia Trial v**s** 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.

NEW
Teflaro™
(ceftaroline fosamil) for injection
600 mg • 400 mg

Demonstrated efficacy in ABSSSI

TEFLARO ABSSSI Study Design[1,3]

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

Study population: 1396 adults with clinically documented complicated skin and skin structure infection

Comparative agents: 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

Treatment duration: Treatment duration was 5 to 14 days. A switch to oral therapy was not allowed

TEFLARO Study Populations

Day 3 Population*

The analysis evaluated patients with lesion size ≥75 cm^2 and having one of the following infection types:
- Major abscess with ≥5 cm of surrounding erythema
- Wound infection
- Deep/extensive cellulitis

Test of Cure (TOC) Populations†

MITT	Modified Intent-to-treat	All randomized subjects who received any amount of study drug.
CE	Clinically Evaluable	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 evaluability 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.
ME	Microbiologically Evaluable	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.

* 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-specified 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.

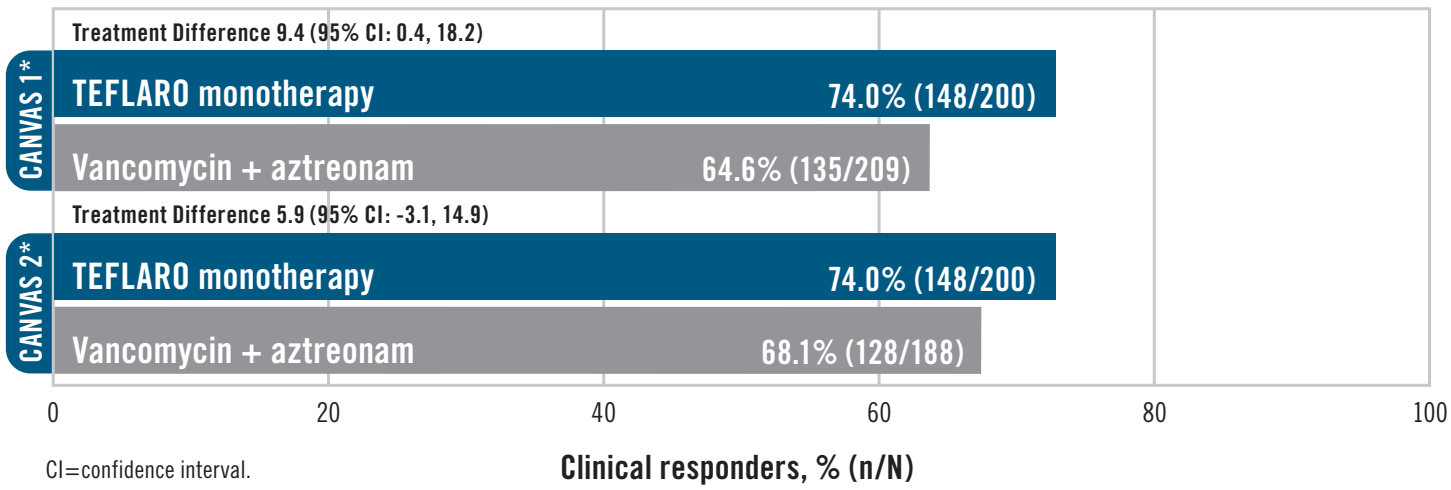
IMPORTANT SAFETY INFORMATION

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[1]

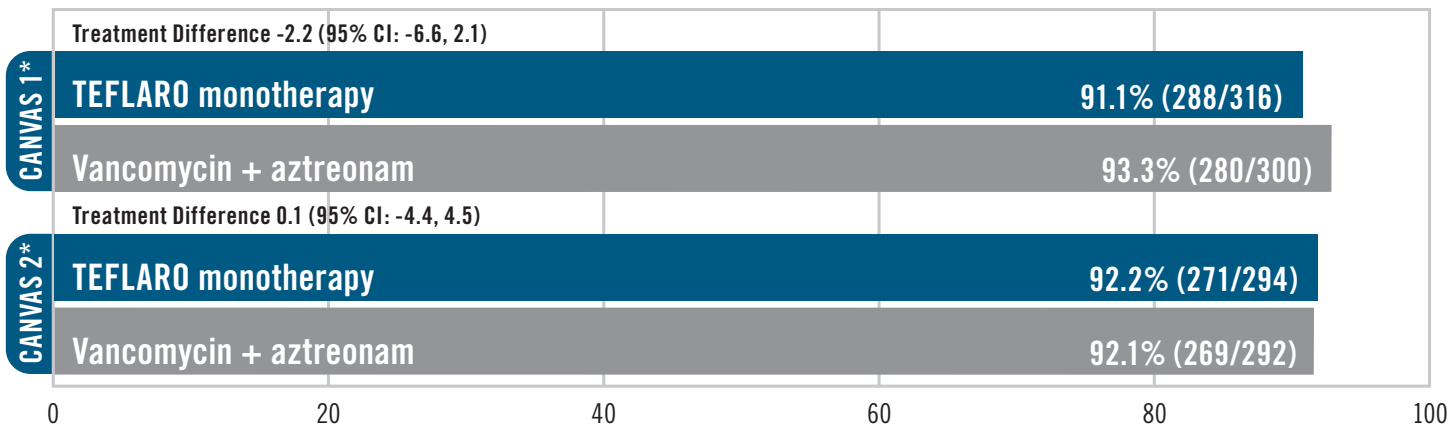


CI=confidence interval.

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[1]



CI=confidence interval.

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

*CANVAS=**C**eft**a**rol**i**n**e** **v**s **V**ancomycin in **S**kin and Skin Structure Infection. CANVAS 1=ABSSSI Trial 1, CANVAS 2=ABSSSI 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 vancomycin plus aztreonam based on clinical response rates at TOC cannot be utilized to establish noninferiority.

References: 1. TEFLARO (ceftaroline fosamil) [prescribing information]. St Louis, MO: Forest Pharmaceuticals, Inc; 2011. **2.** Elixhauser A, Owens P. *Reasons for being admitted to the hospital through the emergency department, 2003*. Healthcare Cost and Utilization Project Statistical Brief #2. February 2006. Agency for Healthcare Research and Quality, Rockville, MD. www.hcup-us.ahrq.gov/reports/statbriefs/sb2.pdf. Accessed February 10, 2011. **3.** Data on file. Forest Laboratories, Inc.

Please see brief summary of Prescribing Information on following page.
Please also see full Prescribing Information at www.TEFLARO.com.

Forest Pharmaceuticals, Inc.
Pharmaceuticals • Therapeutics • Healthcare • Ethicare • Managed Care • Specialty Sales

NEW
Teflaro™
(ceftaroline fosamil) for injection
600 mg • 400 mg

ACCP Guidelines Meet IOM Standards

BY SANDRA ZELMAN LEWIS, PHD; REBECCA DIEKEMPER, MPH; AND JOSEPH ORNELAS, DC, MS, MA

The *Medicare Improvements for Patients and Providers Act of 2008* directed the Institute of Medicine (IOM) to create two committees to provide standards on systematic reviews of comparative effectiveness research and trustworthy clinical practice guidelines. Sandra Zelman Lewis, PhD, of the Health and Science Policy (HSP) staff, was invited to present the American College of Chest Physicians (ACCP) guideline development processes relative to preset questions from the two committees in January 2010. The committee members continued to ask additional questions and included ACCP in a follow-up interview. On March 23, the IOM released two prepublication reports from the Committee on Trustworthy Clinical Practice Guidelines[1] and the Committee on Systematic Reviews.[2]

Dr. Lewis has been invited to the May 10-11, 2011, IOM workshop for guideline developers and systematic reviewers to respond to the reports of these committees. As the ACCP is a society that is considered to produce high quality guidelines, she was requested to "provide examples of how the ACCP is meeting the standards set forth in the reports." The ACCP guidelines currently meet nearly all of the 41 standards. However, there remains room for improvement. Read the full IOM report at www.iom.edu/Reports/2011/Clinical-Practice-Guidelines-We-Can-Trust.aspx.

Intellectual Conflicts of Interest

The HSP has a rigorous process for handling *financial* conflicts of interest. Yet, it does not currently vet or manage *intellectual* conflicts of interest. The Committee permits the individual guideline executive committees to determine if intellectual conflicts will be considered and, if so, how to manage these within the panel operations. Only the *Antithrombotic Therapy and Prevention of Thrombosis: ACCP Evidence-Based Clinical Practice Guidelines, 9th Edition (AT9)* has included intellectual conflicts, thus far. Ironically, the AT9 Executive Committee members collaborated with HSP members and staff to develop and publish the process for handling intellectual conflicts that was touted throughout the IOM report.[3] The HSP will discuss whether to make intellectual conflicts a mandatory part of the conflict of interest policies. Intellectual conflicts are also included in the report on systematic reviews to ensure that the methodologists are free of both intellectual and financial conflicts.

Inclusion of Patients and the General Public

The other major set of standards for guideline development that the ACCP does not meet involves the incorporation of patients in the process. In the past, ACCP guidelines invited participation from patient advocacy groups, but there was a considerable amount of pressure from one advocacy group with an agenda to change a recommendation, even though the evidence did not support that action. The HSP decided at that time to stop inviting patients or patient advocates to participate, allowing instead medical ethicists. Today, there is a program to train these consumers in concepts and techniques of evidence-based medicine, producing consumer (not necessarily patients with the relevant disease or condition) graduates. The HSP is considering including these trained consumers and is, in fact, currently piloting this in one guideline.

The IOM reports go beyond just inclusion of patients/consumers, however, and call for public comment periods for the systematic reviews and guidelines *prior to publication*. Societies that publish guidelines in their journals, like the ACCP, will not be able to meet this standard, as journals will not allow this open posting of the intellectual content until the lifting of the embargo on the date of publication. This will be a discussion point at the May IOM meeting.

Continued on following page

Reminder: Become a OneBreath.org Online Member

Take a moment to participate in The CHEST Foundation's OneBreath™: Make The Most Of It campaign by becoming an online community member. It's as easy as 1, 2, and 3.

1. Go to OneBreath.org. Select the Login link at the top of the page.
2. Use your ACCP ID number as the User ID to simplify logging into multiple College Web sites.
3. To ensure security and assign your membership level, your registration will be processed within 24 hours.

The OneBreath™: Make The Most Of It campaign is a resource for you and your patients. Under the three pillars of education, care, and community, you will find a breadth of content, from patient education materials to prevention and wellness tips. Soon, some content will be focused for certain audiences only. You will need to log in to access that content.

One more thing—we need your help to extend OneBreath's reach exponentially. While accessing OneBreath.org, take a moment to join OneBreath's Facebook and Twitter accounts. Also, encourage your colleagues, patients, family, and friends to become online members and to friend and follow us. Your participation will help make the OneBreath campaign a great success!

Consider Donating Your Honoraria

Did you know that The CHEST Foundation regularly receives honoraria from members involved in teaching ACCP courses around the country? If you are scheduled to present at an upcoming Board Review, Simulation Program, CHEST 2011, or other ACCP educational session, consider donating all or a portion of your honorarium to The CHEST Foundation. Your donation will support The CHEST Foundation's OneBreath™: Make The Most Of It campaign, as we work to engage the public and promote positive health habits and activities that improve lung and heart health.

To donate, contact the ACCP Educational Design and Research Specialist staff overseeing your course, or contact Teri Ruiz at truiz@chestnet.org. Thank you! ■

Webelos Scout Emphasizes Good Lung Health With His Peers

Ten-year old, Dan Carroll, a Webelos scout in the 4th grade at Roaring Brook School in Avon, Connecticut, used components of The CHEST Foundation's Lung Lessons℠ curriculum to give a presentation on lung health and the dangers of tobacco to his peers in Cub Scout Pack 274.

Dan gave this presentation to earn his Fitness Badge. In doing so, he learned more himself and made a special impression on kids his age concerning the effects of smoking.

"I didn't know how dirty and black smoking made your lungs," says Dan. "If more kids saw that, then maybe they wouldn't start smoking. I also didn't know how expensive smoking was before I worked on my presentation."

COURTESY DAN CARROLL

Webelos scout Dan spreading the "good lung health" message.

Dan's father, Dr. Christopher Carroll, FCCP, is Committee Chair for Dan's Cub Scout Pack. Dr. Carroll is Vice-Chair of the ACCP Pediatric Chest Medicine NetWork and serves as Associate Professor of Pediatrics in the Division of Pediatric Critical Care at the University of Connecticut School of Medicine. Dr. Carroll contacted The CHEST Foundation for materials that would assist Dan with his project.

Those interested in teaching good lung health to children, teens, and adults can contact The CHEST Foundation for a variety of materials and tools, which include the Lung Lessons™: A Presenter's Guide and a lending library of teaching aids.

For more information, visit the "Community" section at OneBreath.org, or contact lfulton@chestnet.org. ■

CHEST Journal Goes (More!) Mobile

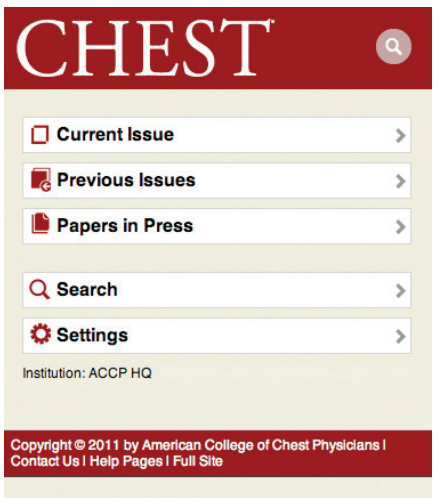
Not just for iPhone®, iPad®, and Kindle™ anymore, *CHEST* is now available for the mobile Web.

Readers can use any Internet-enabled mobile device to access all the latest journal content through the built-in Web browser.

The pared down interface enables browsing of the latest issues and in-press articles, with the full search capabilities of the regular Web site.

The mobile site also features account management functionality, allowing readers to sign up for alerts to the table of contents, just-posted in-press articles, and special sections, such as Topics in Practice Management and Pulmonary and Critical Care Pearls, great for reading on the go.

Give it a try at m.chestjournal.chestpubs.org. ■



Product of the Month

Free Access at http://tobaccodependence.chestnet.org

Tobacco Dependence Treatment Tool Kit (3rd Edition)

Now you can help your patients stop smoking and be reimbursed, using the protocols and coding information contained in this comprehensive tool kit.

The user-friendly, interactive online setting is a complete resource for you and your patients containing background educational materials and clinically relevant instruments to facilitate a highly successful, proven approach to smoking cessation. ■

Continued from previous page

Rigorous Methodological Practices

Independent cross-checking of searches, screenings, and data extractions has been a standard part of a rigorous systematic review for some time. The ACCP has recently hired two skilled staff methodologists, Rebecca Diekemper, MPH, and Joseph Ornelas, DC, MS, MA, who will perform these checks and interrater reliability assessments on a subset of the evidence reviews.

Resources limit the ability to have expert methodologists conduct all of the reviews, so an archived Web series will serve to educate panelists and standardize the methodology.

Finally, these limitations also preclude the ability to have independent third parties manage the peer review process. However, all ACCP guidelines undergo a very thorough and rigorous review from the guideline's executive committee, ACCP NetWorks, HSP, and the Board of Regents, in addition to the standard peer review of the journal.

Thus, of the 41 standards in the two IOM reports, the ACCP clearly meets all but a few. With the careful guidance of the HSP Committee, ACCP guideline processes will continue to improve, evolve, and set examples for other guideline developers. ■

1. Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. Clinical Practice Guidelines We Can Trust. Washington DC: Institute of Medicine, 2011.
2. Committee on Standards for Systematic Reviews of Comparative Effectiveness Research. Finding What Works in Health Care: Standards for Systematic Reviews. Washington DC: Institute of Medicine, 2011.
3. Guyatt G, Akl EA, Hirsh J, et al. The vexing problem of guidelines and conflict of interest: a potential solution. *Ann Intern Med.* 2010; 152(11):738-741.

Electronic Health Records (EHR) Incentive Program and Future Noncompliance Penalty

BY DIANE KRIER-MORROW, MBA, MPH, CCS-P; AND MARLA BRICHTA

The Medicare and Medicaid EHR incentive programs provide incentive payments to physicians (and other eligible professionals) as they adopt, implement, upgrade, or demonstrate meaningful use of certified EHR technology. Physicians who meet the eligibility requirements for both the Medicare and Medicaid EHR incentive programs may participate in only one program and must designate the program in which they would like to participate. Registration for the Medicare EHR incentive program opened on January 3, 2011.

Medicaid EHR Incentive Payment Schedule for Qualified Physicians

Calendar Year (CY)	First CY for Which the Physician Receives an In Incentive Payment					
	2011	2012	2013	2014	2015	2016
2011	$21,250	—	—	—	—	—
2012	$8,500	$21,250	—	—	—	—
2013	$8,500	$8,500	$21,250	—	—	—
2014	$8,500	$8,500	$8,500	$21,250	—	—
2015	$8,500	$8,500	$8,500	$8,500	$21,250	$0
2016	$8,500	$8,500	$8,500	$8,500	$8,500	$21,250
2017	—	$8,500	$8,500	$8,500	$8,500	$8,500
2018	—	—	$8,500	$8,500	$8,500	$8,500
2019	—	—	—	$8,500	$8,500	$8,500
2020	—	—	—	—	$8,500	$8,500
2021	—	—	—	—	—	$8,500
TOTAL	$63,750	$63,750	$63,750	$63,750	$63,750	$63,750

Elsevier Global Medical News

Physicians who do not successfully demonstrate meaningful use of certified EHR technology will be subject to payment adjustments for their covered professional services beginning in 2015.

Medicare EHR Incentive Program

A qualifying physician can receive EHR incentive payments for up to 5 years with payments beginning as early as 2011. In general, the maximum amount of total incentive payments that a physician can receive under the Medicare program is $44,000. A physician will receive an incentive payment equal to 75% of Medicare allowable charges for covered professional services furnished by the physician in a payment year, subject to maximum payments. A physician who predominantly furnishes services in a geographic Health Professional Shortage Area (HPSA) is eligible for a 10% increase in the maximum incentive payment amount. The last year for which a physician can begin receiving incentive payments in the Medicare program is 2014.

Medicaid EHR Incentive Program

The Medicaid EHR incentive program is voluntarily offered and administered by states and US territories. States and US territories can start offering their program to physicians (and other eligible professionals) as early as 2011. The program continues through 2021. For calendar years 2011-2021, participants can receive up to $63,750 over 6 years under the Medicaid EHR incentive program as long as they begin participation in 2016 or before. EHR incentive payments are made by the state based on the calendar year. Medicaid physicians who also treat Medicare patients will have a payment adjustment to Medicare reimbursements starting in 2015 if they do not successfully demonstrate meaningful use.

Registration for the Medicaid EHR incentive program began in early 2011 for several states. At the end of May, the following states already opened registration for their Medicaid EHR incentive program: Alabama, Alaska, Indiana, Iowa, Kentucky, Louisiana, Michigan, Mississippi, Missouri, North Carolina, Ohio, Oklahoma, South Carolina, Tennessee, and Texas. Most states and US territories will launch their Medicaid EHR incentive programs before the end of the year. States and territories had the option of not participating in the Medicaid EHR incentive program, but almost all are scheduled to participate. For your state's/US territory's launch date and Web Site, please see the following Web link: www.cms.gov/apps/files/statecontacts.pdf. ■

NEED ASSISTANCE?

Contact the ACCP coding and reimbursement consultant staff, Diane Krier-Morrow, MBA, MPH, CCS-P at (847) 677-9464 or dkriermorr@aol.com; or contact QualityNet Help Desk: qnetsupport@sdps.org or (866) 288-8912.

Links

2011 Medicare Physician Fee Schedule Final Rule (CMS-1503-FC): edocket.access.gpo.gov/2010/pdf/2010-27969.pdf
CMS EHR Web Page: cms.gov/EHRIncentivePrograms/
List of Eligible Professionals (EPs) for Medicare and Medicaid EHR Incentive Programs: cms.gov/EHRIncentivePrograms/15_Eligibility.asp
List of Certified EHR Technology (CHPL): onc-chpl.force.com/ehrcert

Medicare EHR Incentive Payment Schedule for Physicians

Calendar Year (CY)	First CY for Which the Physician Receives an Incentive Payment				
	2011	2012	2013	2014	2015 and Beyond
2011	$18,000	—	—	—	—
2012	$12,000	$18,000	—	—	—
2013	$8,000	$12,000	$15,000	—	—
2014	$4,000	$8,000	$12,000	$12,000	—
2015	$2,000	$4,000	$8,000	$8,000	—
2016	—	$2,000	$4,000	$4,000	—
TOTAL	$44,000	$44,000	$39,000	$24,000	$0

Elsevier Global Medical News

PCCSU Lessons for May

- **Fixed Airflow Limitation in Asthma.** *By Dr. Anil Ghimire, MBBS; and Dr. Charles S. Dela Cruz, PhD*
- **Sports Activities and Lung Health: Benefits and Risks.** *By Dr. Robert R. Kempainen*

PCCSU Pulmonary, Critical Care, Sleep Update

Pages 24a—24b

SLEEP STRATEGIES

Sleep in America: News From the National Sleep Foundation and the CDC

BY DR. BARBARA PHILLIPS, MSPH, FCCP

Coincident with the loss of sleep that accompanies the change to daylight savings time, the National Sleep Foundation (NSF) and the Centers for Disease Control and Prevention (CDC) released the results of their investigations of America's sleep behaviors during National Sleep Awareness Week (March 7-12).

The National Sleep Foundation 2011 Sleep in America Poll

The NSF poll (http://www.sleepfoundation.org/article/sleep-america-polls/2011-communications-technology-use-and-sleep) focused on sleep and the use of communication technology. This poll included 1,508 surveys (about half of which were Web-based and half of which were by telephone). The respondents were between 13 and 64 years of age. The margin of error for this poll is 2.5 percentage points at the 95% confidence level. In this poll sample, the overall prevalence of sleepiness, defined as an Epworth Sleepiness Scale score (Johns. *Sleep.* 1991;14[6]:540) of 11 or higher, was 13%. There were striking differences by age group, with youngest people being the sleepiest. The prevalence of those with an Epworth Sleepiness Scale score of at least 11 fell from 22% in the 13 to 18 year age group to 9% in those over 46 years.

On average, the participants in the NSF poll reported needing about 7 1/2 h of sleep a night but only getting about 6 h and 55 min of sleep on weeknights. Part of the reason for this sleep gap appears to be electronic technology. Most (95%) of those surveyed use some type of electronic technology (television, computer, video game, or cell phone) at least a few nights a week within the hour before bed. There were striking (but not surprising) differences in these behaviors by age groups. Older people tended to report watching TV more, while younger people were much more likely to report cell phone texting. Cell phones were also reported to disturb sleep, with about 20% of those under the age of 30 reporting that they are awakened by a phone call, text message, or e-mail message at least a few nights a week.

About one-third (37%) of the respondents reported drowsy driving in the past month. This behavior also decreased with age; about half of the youngest (age 19 to 29) drivers reported drowsy driving at least once in the past month, but this was reported by only about 28% of baby boomers. Those who reported drowsy driving were more likely to get less sleep on weeknights, to have Epworth Sleepiness Scale scores of 11 or higher, and to be awakened by cell phones at night.

Dr. James Parish, FCCP
Section Editor,
Sleep Strategies

The CDC Behavioral Risk Factor Surveillance System (BRFSS) Report of Sleep Behaviors 2009

The CDC also released results during National Sleep Awareness Week of a study (McKnight-Eily et al. *MMWR.* March 4, 2011;60[8]) of Americans' sleep behaviors. This report was based on the Behavioral Risk Factor Surveillance System (BFRSS). The BRFSS is a state-based, random-digit–dialed telephone survey of the US adult population. This survey has been conducted by state health departments in collaboration with the CDC for many years. Some components are compulsory and are included annually, and others may be voluntarily included by individual states. California, Georgia, Hawaii, Illinois, Kansas, Louisiana, Maryland, Minnesota, Nebraska, New York, Texas, and Wyoming included an optional sleep module in their 2009 BRFSS, and the data from that module were used to formulate this report. Response rates ranged from 40% in Maryland to 66.9% in Nebraska, and included 74,571 adults.

The questions about sleep (and instructions to the interviewer) were: "On average, how many hours of sleep do you get in a 24-h period? Think about the time you actually spend sleeping or napping, not just the amount of sleep you think you should get (categorized as less than 7 h and greater than or equal to 7 h)." "Do you snore? (can have been told by spouse or someone else; categorized as yes or no)?" "During the past 30 days, for about how many days did you find yourself unintentionally falling asleep during the day (categorized as none or at least 1 day reported)?" and "During the past 30 days, have you ever nodded off or fallen asleep, even just for a brief moment, while driving (categorized as yes or no)?"

About one-third of the respondents (35.3%) reported sleeping less than 7 h on average during a 24-h period. The highest rate of this behavior was in Hawaii (44.6%), and the lowest was Minnesota in (27.6%). People who were at least 65 years old were significantly less likely to report sleeping less than 7 h (24.5%) than persons in any other age categories. Non-Hispanic blacks (48.3%) and non-Hispanic persons of other races (38.7%) were more likely to report sleeping less than 7 h than non-Hispanic whites (34.9%). There were no differences in self-reported sleep duration between men and women. Nonworking adults, those with at least some college education, and single people were significantly more likely to report getting less than 7 h of sleep.

Snoring was reported by nearly half (48 %) of respondents, and its prevalence generally increased with aging. Men (57%) were more likely to report snoring than women (40%).

About 38 % of adults reported unintentionally falling asleep during the day at least once in the preceding month. This behavior was most likely in those between 18 and 24 years and those over 65 years. There were no differences between men and women in the frequency of this behavior. Those who were unemployed, unable to work, or homemakers/students were significantly more likely to report unintentionally falling asleep during the day, but those with at least some college education were less likely to report unintentionally falling asleep than those with less education. Never married adults (43%) were significantly more likely to report unintentionally falling asleep during the day than married adults (36%). Those who reported getting less than 7 h of sleep a night were more likely to report accidentally falling asleep during the day at least once in the previous month.

THOSE WHO GOT LESS THAN 7 H OF SLEEP A NIGHT WERE MORE THAN TWICE AS LIKELY (7.3% VS 3.0%) TO REPORT FALLING ASLEEP WHILE DRIVING.

Nearly 5% of the respondents reported falling asleep while driving in the month before the survey. People who were 65 years or older (2%) were much less likely to report this behavior than persons aged 25 to 34 years (7%). Hispanics, non-Hispanic blacks, and non-Hispanics of other races all were significantly more likely to report drowsy driving than non-Hispanic whites. Men were more likely (5.8%) to say they had fallen asleep while driving compared with women (3.5%). No significant differences were observed by educational level or marital status. Those who reported getting less than 7 h of sleep a night were more than twice as likely (7.3% vs 3.0%) to report falling asleep while driving in the previous month.

Drowsy driving is a significant public health risk, since it puts not just the driver but also those in the car and on the road with the driver at risk. The prevalence of this behavior is not precisely known, and I am not sure that these two data sets help to clarify this issue. The NSF poll and the CDC survey contain divergent information about the frequency of drowsy driving in America, with 5% of those in the BRFSS survey and 37% of those in the NSF poll acknowledging this behavior. This is a big difference, and I am not sure of the reasons for it. The question on the NSF poll was "Thinking of the past month, how many times have you driven a car or motor vehicle while feeling drowsy?" Response options were: 3 or more times a week; 1 to 2 times a week; 1 to 2 times a month; less than once a month; or not at all in the past month. This is not identical to the BRFSS questions ("During the past 30 days, have you ever nodded off or fallen asleep, even just for a brief moment, while driving {categorized as yes or no}?"), but it's remarkably similar. The respondents in the NSF poll were younger and less ethnically diverse than those in the BRFSS sample, which could account for some of the difference. The BRFSS estimate is probably more reliable, since it comes from a much larger sample.

While these data don't tell us precisely how often drowsy driving happens, they do provide insight into the major risk factors. Some are preventable, and some are not. Male gender, non-white race, and youth are the immutable factors associated with drowsy driving in the CDC report, as were being employed and sleeping less than 7 h a night. The NSF poll reinforced the findings that not getting enough sleep and being younger are associated with drowsy driving. The NSF poll confirmed that the Epworth Sleepiness Scale predicts drowsy driving. Indeed, the Epworth Sleepiness Scale is probably the best-documented predictor of sleepiness-related crash risk (Howard et al. *Am J Respir Crit Care Med.* 2004; 170[9]:1014).

The take home message from these reports is that the first step in the workup of the drowsy driver is to ask how much sleep the patient gets at night. Short sleep duration is a more common cause of impaired driving than is obstructive sleep apnea (Pack et al. *Am J Respir Crit Care Med.* 2006;174[4]:446). And our youngest, most inexperienced drivers appear to be at greatest risk. There is considerable concern about cell phone use while driving. The NSF report suggests that cell phone use while sleeping may also increase crash risk! ■

DAVID D. GUTTERMAN, MD, FCCP

PRESIDENT'S REPORT

Evidence-Based Guidelines – A Prominent Jewel in Our Crown

Anticipated with as much enthusiasm, and embargoed with as many safeguards as the winners of the Academy Awards, are the ACCP guidelines. Approximately every 2 to 3 years, there is a palpable ripple in the fabric of medical practice as a major ACCP guideline is released (eg, antithrombotics, lung cancer). In this month's report, I want to describe how the ACCP continues as a pioneer in the development of evidence-based guidelines (EBGs) and how guideline development remains at both the core ***and*** the forefront of our educational mission.

In the summer of 2010, a survey was conducted of almost 5,000 members of the ACCP. When asked about the top five membership benefits (based on importance), the ACCP EBGs ranked number 1, with the *CHEST* journal and the annual CHEST meeting as numbers 2 and 3. Another question asking what influenced members' decision to join the ACCP, up near the top were the EBGs as number 2, following the *CHEST* journal in the number 1 slot. Thus, EBGs form a highly recognized core source of educational support for our members and provide one of the most widely cited publications in support of clinical practice.

One of the reasons that ACCP EBGs are so valuable to our members and others has to do with the rigor used in their development. The College continually updates our guideline development processes, pushing for greater consistency, accuracy, turnaround time, and validity, all while minimizing bias. I was fortunate to serve on the Health and Science Policy (HSP) Committee beginning about a decade ago. Although I went on to chair that committee, were I to apply today, I would be soundly rejected for appointment to HSP. The level of expertise required to successfully participate on the HSP Committee is much greater in 2011. Experience and training in guideline methodology is a prerequisite. Over the past few years, a number of innovations set the ACCP in front with guideline development:

▶ The ACCP requires a detailed listing of all real and potential conflicts of interest by author, cross-referenced for each recommendation. Nominee's conflicts of interest are reviewed by the policies and procedures subcommittee of HSP with development of a management plan if relevant but not overwhelming conflicts are identified. For one recent guideline, 140 nominees were reviewed with 118 approved, 9 of those "with management." Additional panel member suggestions are sought initially due to attrition during the COI process.

▶ In the past few years, the ACCP has implemented an innovative approach[1] by having an nonconflicted methodologist serve as the chapter editor with the content expert (sometimes with a secondary conflict, often intellectual rather than financial) serving as deputy editor. Only the chapter editor and nonconflicted chapter committee members are able to write the actual recommendation. This process prevents potentially conflicted experts from directly influencing the recommendation wording but allows healthy engagement and discussion of the issues.

▶ The ACCP has adopted a standardized process for evaluating evidence, derived from the GRADE Working Group and now uses the ACCP variant of that evidence grading system.[2] This process involves a highly validated-method of literature review to generate evidence tables comparing benefits to risk and assessing the quality of the body of studies. This information is consolidated to provide grades for each recommendation.

▶ We now require a PICO (study characteristics: population, intervention, comparator group, outcome)-style recommendation format. With the 9th edition of the antithrombotics guidelines (AT9), we have incorporated a more globally targeted assessment of resource utilization to fine-tune recommendations and improve their applicability.[3]

▶ Patient values and preferences are included in relevant guideline recommendations to better reflect the preferences of the general population.

▶ We have also added a number of general practitioners to the guideline panel to keep the message of each recommendation relevant and implementable. At the same time, we have sought to format the language of each recommendation in such a way that it best supports the development of performance measures, especially for stronger recommendations.

For future guidelines, HSP and the ACCP are pursuing the concept of a "living guideline" in coordination with

Continued on following page

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the *CHEST* journal. A living guideline exists online and allows recommendations to be updated regularly when new information is published. New data are added to our current evidence tables to determine if a recommendation should change. Coupled with plans to have guidelines exist mostly in an online format, this strategy will allow faster updates, keeping the recommendations fresh.

Our preeminence in the guideline development field has been highlighted by several recent events. First, the ACCP was selected to host the 10th Guidelines International Network conference in August 2010. This was the first such conference held in the United States, and it was a remarkable success. The innovative practices of the ACCP in guideline development were among the highlights of the conference that attracted more than 450 attendees. The ACCP has regularly reported on the innovative changes we have made to our guideline processes. Recent advances in considering patient preferences, development of a new grading system that mirrors GRADE,[2] and a total revamping of our approach to conflict of interest and guideline chapter development[1,4] have been published and have received favorable reviews.[5]

We have also generated the first guideline on delivery effectiveness of continuing medical education.[6] This controversial guideline has broken new ground in the evaluative process used to assess CME.

The clinical impact of EBGs is about to increase dramatically as the US system of health-care reimbursement moves from a "pay-for-procedure" to "pay-for-performance" model. Taking the lead of CMS, third-party payers are implementing the idea that a portion of reimbursement to physicians and hospitals should depend upon outcomes achieved. The logical way to influence practice patterns toward optimal outcomes is to follow scientifically supported practices that have been demonstrated to improve mortality or reduce morbidity. This information is most widely available in published literature, and the most compelling synopsis and practical, clinically useful analysis of these data are in properly conducted evidence-based guidelines. It is, therefore, not surprising that CMS is turning to guidelines produced by societies like the ACCP as a foundation for performance measures to drive reimbursement. The ACCP is positioning itself in the regulatory arena to help the practicing chest physician by ensuring that the right measures are identified by CMS and other payers, for driving reimbursement under a capitated health insurance system.

The ACCP is also moving a step further by organizing quality improvement databases to track physician-specific outcomes. The ACCP now oversees the largest pulmonary interventional database in the world (AQuIRE). This repository of practice and outcomes data can be used to confirm and, when needed, effectively challenge erroneous claims of performance made by third-party payers.

These advances in guideline development that have kept the ACCP at the forefront did not occur spontaneously. They required a coordinated visionary approach by multiple groups within the ACCP. First, and foremost, is the dedication and input of a vigorously active cadre of HSP Committee members, led over the years by Drs. Susan Harding, Michael Baumann, Doreen Addrizzo-Harris, and Ian Nathanson, among others. In addition, Dr. Richard Irwin, Steve Welch, and staff at the journal must be acknowledged for contributing to and facilitating the rapid advances made in the guideline process and supporting the conversion of idea to practice. This has required an unusual degree of flexibility and innovation in publication. Next, special recognition goes to the chairs of our major guidelines. Especially impactful among these are the two most recent leaders of our flagship guideline on antithrombotics and thrombolytics, Drs. Jack Hirsh and Gordon Guyatt. Jack Hirsh has always pushed for innovation and improvement in process and quality. Gordon Guyatt, who took the helm of arguably the most widely cited and disseminated guideline in the world, Antithrombotics 9, stepped up the pace with the novel reforms described above (COI, methodologists as chapter editors, considering patient preference, and resource allocation) that are now being implemented in all of our guideline processes. The medical community will reap the benefits of these advances with the publication of AT9, expected in 2012. Finally, incalculable credit must go to Sandra Lewis, PhD, who effectively conducts this symphony of many parts, aligning workflow, meshing diverse expertise, and otherwise coordinating one of the most complex systems within the College in an unusually effective manner. Everyone who works with Sandy is awed by her breadth of knowledge, sharp focus, and incredible work ethic that are critical to the success of the ACCP guideline effort.

The ACCP was prescient in moving to the forefront of developing EBGs for clinical practice. It is easy to see why guidelines provide the most important value for our members. They effectively cut across our core efforts to provide optimum education for and support the practices of our chest care providers. Even more important, ACCP guidelines provide the most tangible and practical transition from scientific discovery to the day-to-day practice of medicine. We can all be proud of this jewel in our societal crown. ■

1. Guyatt G, Akl EA, Hirsh J, et al. The vexing problem of guidelines and conflict of interest: a potential solution. *Ann Intern Med*. 2010;152(11):738.
2. Guyatt G, Gutterman D, Baumann MH, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians Task Force. *Chest*. 2006;129(1):174.
3. Guyatt G, Baumann MH, Pauker S, et al. Addressing resource allocation issues in recommendations fromclinical guideline panels. *Chest*. 2006;129(1):182.
4. Baumann MH, Lewis SZ, Gutterman D. ACCP evidence-based guideline development: a successful and transparent approach addressing conflict of interest, funding, and patient-centered recommendations. *Chest*. 2007;132(3):1015.
5. Clancy CM, Slutsky JR. Guidelines for guidelines: we've come a long way. *Chest*. 2007;132(3):746.
6. The American College of Chest Physicians evidence-based educational guidelines for continuing medical education interventions: a critical review of evidence-based educational guidelines. *Chest*. 2009;135(3):834.

Correction

In the April issue of CHEST Physician, the following correction should be noted for the first line in "From the CEO": "At CHEST 2010 held in Vancouver, Dr. David Gutterman, FCCP, announced the creation of a Presidential Task Force on Diversity." We apologize for the error.

This Month in *CHEST:* Editor's Picks

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

▶ **Inaccuracy of Doppler Echocardiographic Estimates of Pulmonary Artery Pressures in Patients With Pulmonary Hypertension: Implications for Clinical Practice.**
By Dr. J. D. Rich et al.

▶ **The Effect of Supplemental Oxygen on Hypercapnia in Subjects With Obesity-Associated Hypoventilation: A Randomized, Crossover, Clinical Study.**
By Dr. M. Wijesinghe et al.

▶ **Changes in Heart Rate Variability After Adenotonsillectomy in Children With Obstructive Sleep Apnea.**
By Dr. H. V. Muzumdar et al.

CONTEMPORARY REVIEWS IN SLEEP MEDICINE

▶ **Sleep Medicine Training Across the Spectrum.** *By Dr. K. P. Strohl.*

FROM THE DESK OF THE PRACTICE MANAGEMENT COMMITTEE

Introduction to RUC

BY ROBERT DEMARCO, MD, FCCP, CHAIR; AND DONNA KNAPP BYBEE, MA, FACMPE, VICE-CHAIR

In April's *CHEST Physician*, we discussed *Current Procedural Terminology* (CPT®). Now, we turn to the American Medical Association (AMA)/Specialty Society RVS Update Committee (RUC), a committee that makes recommendations regarding physician work and practice expense relative values to the Centers for Medicare & Medicaid Services (CMS). The relative values are a unit of measure of the Resource-Based Value Scale (RBRVS) and are based on the resource costs of procedures defined in the CPT. All relative value units (RVUs) must be reviewed at least every 5 years.

The RUC is made up of 29 members, 23 of whom occupy permanent seats appointed by certain major national medical specialty societies. Some permanent seats are held by those societies whose specialties accounts for a high percentage of Medicare expenditures. Other permanent seats are held by specialty societies to represent large numbers of physicians caring for Medicare beneficiaries or to represent essential specialty perspectives (eg, pediatrics). Pulmonary medicine currently holds one of the two Internal Medicine rotating seats. We are represented by Dr. Scott Manaker, PhD, FCCP, and his alternate, Dr. Alan Plummer, FCCP. All rotating seats are held for 2-year terms.

The RUC Advisory Committee, with broader specialty representation than RUC itself, is made up of one physician representative from each of the 110 specialty societies seated in the AMA House of Delegates. Dr. Burt Lesnick, FCCP, is ACCP's representative on the RUC Advisory Committee. RUC advisors and their corresponding specialty societies are responsible for generating relative value recommendations using a survey method developed by the RUC. Advisors and specialty staff attend RUC meetings, with advisors presenting their societies' recommendations for evaluation.

As with CPT issues, the ACCP Practice Management Committee (PMC) also represents ACCP members' interests regarding the RUC process. The ACCP PMC communicates level of interest in CPT codes under review, conducts surveys, reviews survey results, and prepares recommendations regarding physician work and practice expense to the RUC. The PMC also represents ACCP in several other ways, including representing ACCP Members' interests regarding CPT.

A Summary of the RUC Process

1. The RUC prepares a "Level of Interest" form, summarizing the CPT Editorial Panel's new and revised codes.
2. The RUC Advisory Committee members and specialty society staff indicate ACCP's level of interest in developing relative value recommendations on the "Level of Interest" form.
3. The AMA distributes survey instruments to the specialty societies.
4. Specialty society committees (eg, ACCP PMC) conduct the survey, analyze the results, and prepare a recommendation for the RUC.
5. The specialty society advisor presents the recommendation at the RUC meeting.
6. The RUC decides to forward a specialty society's RVU recommendation to CMS unchanged, to make modifications to the recommendation before forwarding to CMS, or to refer the recommendation back to the specialty society for further consideration.
7. CMS makes their final valuation decision and publishes the decision in the *Medicare Physician Payment Schedule* in the fall of each year. ■

Example of CPT Code With National Values

Code	Descriptor	Physician Work (Work RVU)	Non-Facility Practice Expense (PE RVU)	Physician Liability Insurance (PLI)	Total RVU (Non-Facility)	Medical Non-Facility Payment (National)
99213	Evaluation and management, level 3, established patient	0.97	0.99	0.07	2.03	$68.97

CY 2011 RVU Conversion Factor Rate = $33.9764

CHEST 2011: Designed With Hawaii in Mind

CHEST 2011 is designed to feature a clinical learning program in pulmonary, critical care, and sleep medicine, while also allowing you to take in the Hawaiian experience. Programs and sessions will start earlier than previous years and end by mid-afternoon, giving you time to enjoy the tropical setting. General sessions end October 26, and after-CHEST postgraduate courses begin October 28, leaving Thursday, October 27, as a day for you to spend as you wish.

CHEST 2011
October 22 - 26
Honolulu, Hawaii

Plan to take advantage of these program features:

Postgraduate Multipass Courses and Additional Courses

Saturday, October 22

Attend postgraduate multipass courses for focused study on specific topics. Registration will allow a multipass to any postgraduate multipass course.

Additional courses, separate from the postgraduate multipass courses, will be offered also. Registration to these courses will not permit admittance to other courses.

A flash drive containing course material for all courses, excluding the ABIM SEP modules, will be given to all attendees of the Saturday courses.

General Sessions

Sunday, October 23 – Wednesday, October 26

Choose from more than 300 sessions to advance your education in clinical chest medicine. Take advantage of simulation learning in the ACCP Simulation Center and small group, interactive instruction in problem-based learning sessions. Be sure to attend the opening global session and keynote address, each addressing a timely topic in clinical chest medicine.

After-CHEST Postgraduate Courses

Friday, October 28 – Saturday, October 29

Keep your learning momentum going at three after-CHEST postgraduate courses—offered on Maui, Hawaii, or Oahu—providing the opportunity to earn additional CME and visit neighboring islands.

After-CHEST postgraduate courses will be held 7:00 AM to 12:35 PM each day, so you can attend the course in the morning, and enjoy Hawaii in the afternoon.

CHEST 2011 registration and housing are open. Act now to take advantage of early registration fees and the best hotel selection—**www.accpmeeting.org.** ■

NETWORKS
Affiliates' Survey, Step-down Asthma Therapy, Codes

Affiliate

Fellows' Focus: Results of the 2010 Fellows' Survey

In 2010, the Affiliate NetWork Steering Committee conducted a confidential and anonymous survey of fellows asking them to evaluate their fellowship training experience, share their career plans, and inform us of ways in which the College could assist them with meeting their educational and career goals.

Of the 115 respondents, approximately two-thirds (64.8%) planned on pursuing careers in academic medicine; most finding their calling as clinician-educators (40.5%), and two-thirds (66%) aspiring to become future leaders of the College.

Although most fellows (80%) believed that their training program met their expectations, a majority of respondents felt that they had insufficient experience in the following areas: endobronchial ultrasound (EBUS) (60.9%), interventional bronchoscopy (58.2%), lung transplant (56.4%), neuro-critical care (55%), and pulmonary rehabilitation (50.9%).

The top three choices highlighted for additional Affiliate NetWork Web site features were: a recommended reading list on clinical subjects; online case submissions that could be considered "e-publications"; and career guides (94.2%, 83.5%, and 82.4%, respectively, rated these as a 4 or 5 on a 5-point scale).

While the role and responsibilities of our committee continually evolve, our primary goal remains the education, welfare, and professional development of our trainees. ACCP's Affiliate NetWork will utilize the feedback constructively by exploring new and innovative educational programs and resources that will enhance educational and career goals. Such programs will include the introduction of novel NetWork Highlight sessions and simulation training during the annual meeting and implementation of inventive resources and learning modules to the NetWork Web site.

Dr. Nader Kamangar, FCCP, Vice-Chair; and Dr. John D. Buckley, FCCP, Chair

Airways Disorders

Step-down Therapy in Asthma: What Is the Optimal Approach?

Current asthma guidelines recommend a step-up approach when using pharmacologic therapy to control asthma and then stepping down therapy once asthma control is maintained for at least 3 months. Reducing treatment is straightforward in those using inhaled corticosteroids (ICS) alone, but the optimal approach to reducing therapy in patients with moderate to severe asthma treated with combination ICS and long-acting beta-agonists (ICS/LABA) is unclear, especially since controversy over the safety of LABAs continues.

In February 2010, the US Food and Drug Adminstration recommended that LABAs should be used for the shortest time needed to achieve asthma control and then be discontinued. These recommendations did not specify timing of such an approach to adding and stepping down therapy, and this issue has not been well studied in clinical trials. This has left clinicians confused as to how to best approach step-down of ICS/LABA-treated patients, since currently available data suggest that the preferred strategy is to reduce the ICS dose prior to discontinuing the LABA (Fowler et al. *J Allergy Clin Immunol*. 2002;109[6]:929; Bateman et al. *J Allergy Clin Immunol*. 2006;117[3]:563; Reddel et al. *Respir Med*. 2010;104[8]:1110; Godard et al. *Respir Med*. 2008;102[8]:1124). So, do these studies answer this question definitively? Unfortunately, the answer is no. These studies were of limited duration, so it is unclear if asthma control was maintained following de-escalation of treatment. Moreover, not all of these studies ascertained that patients remained symptomatic receiving low to moderate dose ICS alone, and were, thus, treated according to current recommendations for use of LABAs. Further studies that compare these two different strategies for step-down therapy in moderate to severe asthma appear warranted.

Dr. Linda Rogers, FCCP Steering Committee Member

Interventional Chest/Diagnostic Procedures

Collaboration in Interventional Pulmonology

Interventional pulmonology (IP) is an emerging field within pulmonary medicine with focus on minimally invasive techniques for the diagnosis and management of lung cancer, central airway obstruction, and pleural disease (Wahidi et al. *Chest*. 2007; 131[1]:261). The advent of interventional pulmonologists into medical centers has been met with various reactions among physicians from different specialties; while some saw an opportunity for collaboration and enhancement of patient's outcome, others viewed it as a threat to their practice and opted to take a hostile stand.

The most important relationship for IP is that with thoracic surgery (TSU). These two specialties commonly share patients with clinical quandary, such as staging of lung cancer with endobronchial ultrasound or mediastinoscopy, diagnosis of the peripheral lung nodule with bronchoscopy or surgical resection, and approach to pleural disease with a variety of sampling techniques, including medical thoracoscopy or video-assisted thoracoscopic surgery. Interventional pulmonologists need the surgical back-up of the thoracic surgeon and the access to advanced surgical interventions for their patients. Similarly, the thoracic surgeons benefit from the availability of an advanced bronchoscopist and dedicated clinician with appropriate referrals for surgical resection.

Ultimately, the ideal approach should be one of multidisciplinary collaborative care, where IP and TSU share patients, thoughts, tools, and support. The overarching goal is to achieve the best patient outcome employing the safest and most effective patient-centered medical care. We call on our colleagues to extend a hand to each other, and join forces to create shared value for all involved parties.

Dr. Momen Wahidi, MBA, FCCP, Vice-Chair; and Dr. Kazuhiro Yasufuku, PhD, FCCP, Steering Committee Member

Pulmonary Physiology, Function, and Rehabilitation

Reporting Update for Pulmonary Function Testing and Pulmonary Rehabilitation

There is a significant number of recent changes that directly impact reporting for procedures, such as pulmonary function testing (PFT) and pulmonary rehabilitation. Relevant current changes include the addition of Category III tracking codes, 0243T and 0244T. These codes are to be reported for administering acoustic PFTs, which as the name implies, are codes gathered by payers to track the utilization of new technologies not currently reimbursable. Category II codes are used to report performance measures that are reported in addition to the usual CPT® Category I code. The reporting of these codes is required to qualify for PQRS incentive payments from Centers for Medicare & Medicaid Services. Pulmonary performance measure 51 is specifically to be used along with spirometry evaluation codes (**94010**, **94375**, or **94060**) for patients aged 18 years and older with a diagnosis of COPD who had spirometry results documented. The additional CPT® Category II code reported is **3023F** "Spirometry results documented and reviewed."

Pulmonary rehabilitation, the standard of care for treatment of COPD, is clearly now ready for prime time. Medicare coverage for this important therapy is now available to all qualifying beneficiaries. A notification mailed to all Medicare beneficiaries clearly indicates coverage for comprehensive pulmonary rehabilitation (HCPCS G0424) for moderate to very severe COPD (*Medicare and You*. 2011; 41). Recently, the approved diagnosis list has been expanded beyond moderate to very severe COPD by Highmark Medicare Services Local Coverage Determination (LCD) L31483. Effective for services performed on or after March 22, 2011, the expanded diagnosis includes cystic fibrosis (277.00), asthma (493.10-493.91), bronchiectasis (493.10-493.91), and a variety of other diagnoses. It is anticipated that other Medicare Administrative Contractors (MAC) will emulate the Highmark LCD.

Sam Birnbaum, CMPE Steering Committee Member

Pulmonary Vascular Disease

Providers who treat pulmonary vascular disease (PVD) or exertional dyspnea routinely face complex cardiopulmonary hemodynamic interactions. These articles discuss predictors of pulmonary hypertension (PH) severity, right ventricular (RV) performance, and hemodynamic response to exercise in patients with dyspnea.

Arkles and colleagues (*Am J Respir Crit Care Med*. 2011;183[2]:268) describe the correlation of elevated pulmonary vascular resistance and RV systolic dysfunction in patients with PH who demonstrated systolic deceleration or "notching" of the RV outflow tract Doppler flow velocity envelope on echocardiogram. "Notching" appears to represent a pathologic wave reflection in the setting of elevated pulmonary artery impedance. Those with midsystolic notch had the most severe PVD and RV dysfunction. This could have clinical implications, especially if "notching" can be easily identified by less experienced echocardiogram readers.

Groepenhoff and colleagues (*Eur J Heart Fail*. 2010;12[7]:716) discuss differences in the ability to increase cardiac output (CO) between patients with left heart failure (LHF) vs patients with pulmonary arterial hypertension (PAH). About 42% of both groups had impaired exercise tolerance on a maximal cardiopulmonary exercise test. The PAH group had significantly lower peak stroke volume (SV) response to exercise (-14 mL, $P = 0.01$) but had a larger HR response to increased CO. This finding highlights potential detrimental effects of beta-blockers in PAH.

Plehn and colleagues (*Acta Cardiol*. 2009;64[5]:617) evaluated patients with normal left heart performance by echocardiogram and exertional dyspnea with suspected left ventricular (LV) diastolic dysfunction (DD) as its cause. An exercise challenge performed during right-sided heart catheterization led to abnormal elevation of capillary wedge pressure in 74% of subjects. Peak CO response was reduced mainly because of impaired increase in SV. Invasive exercise hemodynamics can help unmask LVDD in patients with dyspnea.

Dr. Francisco Soto, FCCP Chair

Maximize Your Access to Federal Money for EHRs

BY DAMIAN McNAMARA
Elsevier Global Medical News

FORT LAUDERDALE, FLA. – The U.S. government provides up to $63,750 per qualified health care provider as an incentive toward "meaningful use" of electronic health records.

"The money is there, but you have to jump through a lot of hoops to get it," said Dr. Burt Lesnick, FCCP.

The program started this year, so those physicians who registered in January will start to receive payments in May 2011. You can use the money to purchase, implement, and/or maintain an electronic health record (EHR) system.

The funds also can go toward training staff to use the EHR, said Dr. Lesnick, a private practice pediatric pulmonologist and managing partner of Georgia Pediatric Pulmonary Associates in Atlanta.

You must apply for this stimulus funding between now and 2016, and your practice must meet multiple criteria. For example, at least 30% of your patients must meet a "needy threshold" or be Medicaid recipients.

"If you are a typical pediatric pulmonologist in the United States, you are taking care of a lot of Medicaid patients," Dr. Lesnick said at a seminar on pediatric pulmonology sponsored by the American College of Chest Physicians and the American Academy of Pediatrics.

Physicians have to document 15 core measures and at least 5 of 10 optional measures to receive the funds.

The government provides the funds over 5 years, Dr. Lesnick said, "so there is no immediate need to start using them."

The 15 core measures you must document to demonstrate meaningful use are:

- ► Computerized provider order entry is used.
- ► Drug-drug and drug-allergy interaction checks are done.
- ► Up-to-date problem list of current and active diagnoses is maintained.
- ► Electronic prescribing is utilized.
- ► Active medication list is kept.
- ► Active medication allergy list is kept.

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Pulmonary/CC Positions

METRO SOUTH CAROLINA: Hospital employed nine physician group with 420 bed health system two hours to Atlanta/Charlotte 1-10 call. **PORTLAND SUBURBS**: Hospital employed in Portland suburbs with modern 167 bed hospital. light 1-2 call. Excellent salary, bonus, benefit package. 800-831-5475 F: 314-984-8246 E/M: donohueandassoc@aol.com.

Pulmonary/Critical Care Physician

Peoria, IL - Pulmonary/Critical Care physician to join OSF Saint Francis Medical Center, a Level 1 Trauma Center and major referral center to 23-county region, is affiliated with the University of Illinois College of Medicine. Call or send CV to: Rachel Reliford, Phone: 309-683-8352 Email: rachel.reliford@osfhealthcare.org Web: www.osfhealthcare.org.

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For information contact: **Wendy Castaldo, Director of Medical Staff Development, Upper Valley Medical Center, 1-800-772-3627, FAX: 937-440-8549, wcastaldo@uvmc.com (J-1 Visa waiver not available)**

TWO DAY REVIEW COURSE
HANDS ON EXPERIENCE / TRAINING
HELPFUL FOR ABIM BOARD CERTIFICATION IN SLEEP MEDICINE

Saturday, July 23 and Sunday, July 24, 2011
8:00am – 6:00pm
Venue: Sleep Disorders Center of Elizabethtown
Elizabethtown, Kentucky

Who will benefit:
Physicians taking Practice Pathway Exam
Physicians requiring Practical Experience for Exam
Physicians needing experience to score, review and interpret sleep studies

**** This will be an excellent opportunity to enhance the knowledge and prepare for the Exam ****

Board Certified Sleep Physicians; Fully Trained and Registered Polysomnography Techs will be available to assist and train the participants.

Program includes:
Didactic Lectures, Hand on Experience and Practice Questions
(CME Credit will be provided)

This is a focused training course intended to review requirements for completing the exam. Course participants will be responsible for their lodging and food. Lunch will be provided during the course.

For more information or to register,
Contact Amanda Swift at 270-765-2459 (between 9am – 5pm)
or email ayazdanipulmonologist@yahoo.com

Program Fee $900.00
Administration has the right to cancel the course at any time without any reason, with full refund. Participant cancellation fee of $50 for Administrative cost will be deducted from the program fee refund.

Sponsors:
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Hunterdon Medical Center, located in Flemington, New Jersey, has an outstanding opportunity for a board eligible or certified pulmonary medicine, critical care, and sleep medicine physician to join a group of 3 full time physicians in a hospital employed practice. Hunterdon Medical Center is a 178 bed community teaching hospital with a 12 bed intensive care unit.

The responsibilities will include sharing in providing care in the intensive care unit, sleep lab, inpatient pulmonary service, inpatient pulmonary consultation and outpatient pulmonary practice.

The medical center offers an excellent compensation and benefits package. The community is a beautiful area of small towns and rolling countryside in which to live and raise a family. We are located about 1 hour from NYC and Philadelphia.

Interested candidates should apply on-line at www.hunterdonhealthcare.org

► Demographics are recorded.
► Vital signs are recorded in chart.
► Smoking status is recorded for all patients older than 13 years ("I'm excited about this one," Dr. Lesnick said. "We need to ask them, hopefully in a private setting without their parents, if they are smoking cigarettes, which is far overdue as far as I'm concerned.").
► Ambulatory clinical quality measures are reported to the Centers for Medicare and Medicaid Services.
► At least one clinical decision support rule is implemented.
► Patients are provided with an electronic copy of their health record.
► Patients are provided with a clinical summary of their visit (most EHR systems feature a portal where patients can log in to review password-protected records, Dr. Lesnick said).
► Electronic information has privacy safeguards.

You also are required to document five of the following optional measures:
► Drug formulary checks are done.
► Clinical lab results are recorded as structured data.
► Reminders are sent to patients by their preferred method.
► Patient lists can be generated by diagnosis.
► The system is capable of exchanging key clinical information between providers of care and other authorized entities.
► Patients are given timely access to their health information.
► The EHR system is used to provide health education for your patients.
► Medication reconciliation is provided.
► A summary of care record for patient transitions is provided.
► Immunization data can be submitted to registries (in the state where Dr. Lesnick practices, this is called the Georgia Registry of Immunization Transactions and Services, or GRITS).
► Surveillance data is in a format that can be submitted to public health agents.

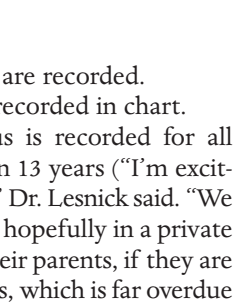
PHYSICIANS HAVE TO DOCUMENT 15 CORE MEASURES AND AT LEAST 5 OF 10 OPTIONAL MEASURES TO RECEIVE THE FUNDS.

"In addition to all that, there have to be six clinical quality measures," Dr. Lesnick said. Asthma assessment, hypertension screening, and initiation and engagement of alcohol and other drug dependence treatment are among the choices on a list of 47 prespecified measures.

Despite the many requirements for funding and implementation of an EHR, "ultimately, it will make all of us better physicians," he said.

Dr. Lesnick had no relevant financial disclosures. ■

COMMENTARY



Dr. Stuart Garay, FCCP, comments: It is extremely important for everyone to "get their act together" in acquiring electronic health records (EHRs). However, most of the pediatric pulmonologists in my area have less than 30% of their patients as Medicaid recipients and do not participate with Medicaid.

Thus these physicians would not qualify for government incentives.

In addition, without a significant Medicare population, they do not qualify for the federal incentive money for doctors participating with Medicare.

Also, a point mentioned only in passing is the need to have a system that can share data with Health Information Exchanges (HIEs), hospitals, and labs.

A big question is who pays for this linkage (hospital, vendor, or doctor) and making sure that your EHR will provide this capability.

This is one more wake-up call for those physicians who have not begun to consider implementing an EHR.

Most of the requirements for "meaningful use" to qualify for Medicare patients are the same as Medicaid's, but the Medicare total incentive is less, at $44,000.

TYGACIL is in the IDSA/SIS guidelines for cIAI and the SIS guidelines for cSSSI.[1,2]

Expanded broad-spectrum coverage[3]* is on your side

***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-anabolic 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.

References: 1. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Clin Infect Dis*. 2010;50(2):133-164. **2.** May AK, Stafford RE, Bulger EM, et al. Surgical Infection Society Guidelines: Treatment of complicated skin and soft tissue infections. *Surg Infect*. 2009;10:467-499. **3.** TYGACIL® (tigecycline) Prescribing Information, Wyeth Pharmaceuticals Inc.

Pfizer

Tygacil® tigecycline IV

Expanded broad-spectrum coverage