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COURTESY ACCP

Welcoming the New ACCP President

Dr. David G. Gutterman, FCCP, left, passes the presidential gavel to Dr. Suhail Raoof, FCCP. See pages 26-27 for more highlights from CHEST 2011 in Honolulu.

Jury Still Out on Steroids for ALI-ARDS

BY DOUG BRUNK
Elsevier Global Medical News

HONOLULU – The jury is still out on whether patients with acute lung injury and adult respiratory distress syndrome derive any benefit from the use of corticosteroids, Dr. Stephen M. Pastores, FCCP, said at CHEST 2011, the annual meeting of the American College of Chest Physicians.

"This is probably the most controversial topic in acute lung injury and ARDS," Dr. Pastores of the department of anesthesiology and critical care medicine at Memorial Sloan-Kettering Cancer Center, New York. "Those of us who believe in the use of corticosteroids base that on the pretty good evidence that they are effective anti-inflammatory agents. There have been a few positive trials for the use of prolonged corticosteroid treatment in ALI [acute lung injury]–ARDS, with significantly less side effects in comparison to older trials investigating massive doses," such as methylprednisolone 120 mg/kg per day.

Renewed interest in this topic came about 4 years ago, he said, after publication of a study that evaluated the effects of low-dose methylprednisolone infusion on lung function in 91 patients with early ARDS (within 72 hours). About two-thirds of the patients (66%) had sepsis (Chest 2007; 131:954-63). Patients were randomized to receive methylprednisolone infusion (1 mg/kg per day) or placebo for up to 28 days. The primary end point was a 1-point reduction in the lung injury score or successful extubation by day 7.

"An important piece of this study was that [the researchers]

See **ALI-ARDS** • *page 4*

Sildenafil Found Beneficial in Pediatric PAH

Peak V_{O_2} and V_E/V_{CO_2} slope improved.

BY DOUG BRUNK
Elsevier Global Medical News

HONOLULU – The use of oral sildenafil helped improve oxygen delivery and exercise capacity in children with pulmonary arterial hypertension, results from a randomized, multicenter trial showed.

The study, which employed cardiopulmonary exercise testing – including assessment of ventilation to carbon dioxide (V_E/V_{CO_2}) slope – "confirmed our suspicion that ventilatory efficiency, as measured by V_E/V_{CO_2}, appears to be a sensitive measurement to assess exercise ability in pediatric pulmonary arterial hypertension as long as the children are old enough and developmentally able to exercise reliably," lead investigator Dr. Robyn J. Barst, FCCP, said in an interview in advance of CHEST 2011, where the study was presented. Using such measures may allow future trials to determine drug effectiveness and safety with fewer study participants, thus shortening time to approval for new drugs, she said.

The STARTS-1 study included 234 treatment-naive children with pulmonary arterial hypertension (PAH), who were aged 1-17 years and weighed 8 kg or more. Participants were randomized to receive placebo or low, medium, or high doses of oral sildenafil three times a day at 1 of 32 centers in 16 countries, including the United States. Doses were based on weight groups – 8-20 kg, 20-45 kg, and more than 45 kg – with the doses ranging from 10 to 80 mg t.i.d. Sildenafil is approved in the European Union for children with PAH at a dose of 10 mg t.i.d. for children who weigh less than 20 kg and 20 mg t.i.d. for children over 20 kg, but is not currently

See **Sildenafil** • *page 13*

CFRD Is Not Your Typical Diabetes

BY KERRI WACHTER
Elsevier Global Medical News

BALTIMORE – Cystic fibrosis–related diabetes differs from type 1 and 2 diabetes and requires different management.

"Screening early and knowing which patients are at risk is really important," Amanda Leonard said at a meeting on pediatric nutrition sponsored by Johns Hopkins University.

Pulmonary function begins to decline several years before diagnosis of cystic fibrosis–related diabetes (CFRD), so identifying and treating patients with CFRD can have a big impact on life expectancy, said Ms. Leonard, a senior pediatric clinical dietician at the Johns Hopkins Cystic Fibrosis Center.

Although CFRD is very different from type 1 and type 2 diabetes, "it does share some components," she said. She summarized the highlights of the clinical care guidelines for CFRD issued by the American Diabetes Association and the Cystic Fibrosis Foundation (Diabetes Care 2010;33:2697-708).

CFRD is associated with

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NEWS FROM THE FDA

CFC-Free Inhaler for COPD Approved

An inhalation spray containing ipratropium bromide and albuterol sulfate has been approved for patients with COPD, according to a statement by the Food and Drug Administration.

The product, marketed as Combivent Respimat inhalation spray, does not contain chlorofluorocarbons (CFCs) and "is a suitable alternative for patients who are currently using Combivent (ipratropium bromide and albuterol sulfate) inhalation aerosol," according to the statement, issued by the Division of Drug Information (DDI) in the FDA's Center for Drugs, Evaluation and Research (CDER). Combivent inhalation aerosol, which contains CFCs, will not be available after Dec. 31, 2013. Like other inhalers that contain CFCs that deplete the ozone layer, the inhaler is being phased out because of the Montreal Protocol on Substances that Deplete the Ozone Layer, which makes it illegal to sell or make substances that decrease the ozone layer.

Ipratropium is an anticholinergic bronchodilator, and albuterol is a selective beta-2 adrenergic bronchodilator. Combivent inhalers are indicated for people with COPD on a regular bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator.

PAH Risk Seen With Dasatinib

Treatment with the leukemia drug dasatinib has been linked with an increased risk for pulmonary arterial hypertension, which can occur at any time after starting treatment, the FDA announced. None of the cases were fatal, and PAH "may be reversible" if treatment is discontinued, according to the statement.

Dasatinib, a kinase inhibitor marketed as Sprycel by Bristol-Myers Squibb, is approved for treating adults with Philadelphia chromosome-positive chronic myeloid leukemia (CML) or acute lymphoblastic leukemia (ALL). Since dasatinib was approved in 2006, the BMS global pharmacovigilance database has identified cases of PAH in treated patients, the statement said. In 12 of these cases, right heart catheterization confirmed the diagnosis, and dasatinib was considered "the most likely cause," the FDA said. These patients had developed symptoms at various intervals after starting treatment, including more than 12 months afterward, and they often were taking other medications or had comorbidities, so "there may be a combination of factors contributing to the development of PAH" in patients taking dasatinib, the FDA said.

Because dyspnea, fatigue, hypoxia, fluid retention, and other PAH symptoms overlap with those of other conditions, "a diagnosis of Sprycel-associated PAH should be considered" if other causes have been ruled out in symptomatic patients, the FDA advises. Health care professionals should also evaluate patients for signs and symptoms of underlying cardiopulmonary disease before and during treatment. The drug should be permanently discontinued if a diagnosis of PAH is confirmed. Improvements in hemodynamic and clinical parameters were observed following discontinuation in some patients, the FDA statement said.

Risks Added to Bevacizumab Label

A warning about the risk of ovarian failure in premenopausal women has been added to the label for bevacizumab, along with additional data about venous thromboembolic events and new postmarketing data identifying osteonecrosis of the jaw as an "adverse reaction," the FDA said.

Bevacizumab – marketed as Avastin by Genentech – is a vascular endothelial growth factor inhibitor approved in 2004 for the treatment of lung and several other cancers. (Approval for use in breast cancer was revoked by the FDA on Nov. 18.)

Information about the increased risk of VTEs and bleeding associated with bevacizumab in patients receiving anticoagulation therapy after a first VTE event has also been added in the section on Clinical Trial Experience, the FDA said. A randomized, prospective four-arm study of 1,401 patients found that in those in the bevacizumab-containing arms, the incidence of a first VTE was 13.5%, compared with 9.6% among the patients in the chemotherapy-only arms.

The potential for ovarian failure associated with bevacizumab treatment is new information. The label now states that the long-term effects of exposure to bevacizumab on fertility are unknown and that women of reproductive potential should be informed about the risk of ovarian failure before starting treatment.

The label also now includes a statement about postmarketing reports of osteonecrosis of the jaw (ONJ) in patients treated with bevacizumab who have not been treated with bisphosphonates. (ONJ has been reported in patients on bisphosphonates.)

Septic Shock Drug Pulled Off Market

The failure of Xigris to show an effect on mortality in a clinical trial of patients with septic shock has prompted the manufacturer to withdraw the drug from the United States and other countries where it is approved, Eli Lilly announced.

Xigris (drotrecogin alfa [activated]), a recombinant form of human activated protein C, was approved in the United States in 2001 for the reduction in mortality in adults with severe sepsis who have a high risk of death.

The PROWESS-SHOCK study showed that treatment with Xigris did not meet the primary end point, a significant reduction in 28-day all-cause mortality in patients with septic shock, Lilly announced in a statement.

"While there were no new safety findings, the study failed to demonstrate that Xigris improved patient survival and thus calls into question the benefit-risk profile of Xigris and its continued use," Dr. Timothy Garnett, senior vice president and chief medical officer at Lilly, said. Xigris should be stopped in patients currently being treated with it, and the drug should not be used in new patients.

–Elizabeth Mechatie

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Criteria Shift for Lung Transplantation Candidacy

BY DOUG BRUNK
Elsevier Global Medical News

HONOLULU – Not long ago, patients older than 65 years were rarely considered candidates for lung transplantation. But that's not quite true anymore.

Being elderly is still a relative contraindication, but according to data from the International Society for Heart and Lung Transplantation, an increasing proportion of people older than age 65 are receiving lung transplants, from about 2% in 1995-1999 to about 6% between 2000 and June 2010.

Instead of age and the length of time spent on the list waiting for a transplant, candidacy for the procedure is now based on whether patients' advanced respiratory disease has progressed despite medical therapy, and whether they have a 50% or less chance of survival in the next 2-3 years, Dr. Luis F. Angel, FCCP, explained at CHEST 2011.

"Potential candidates must be capable of comprehending the procedure, undergoing the selection process, and waiting the time necessary on the waiting list," said Dr. Angel, director of lung transplantation at the University of Texas Health Science Center at San Antonio.

In a review of the latest criteria, he explained that patients "must also be free of significant medical comorbidities and be sufficiently fit to handle this major surgical procedure and multiple medications post procedure."

The list of absolute contraindications for lung transplantation is lengthy, and includes recent malignancy (other than nonmelanoma skin cancer); infection with HIV; infection with hepatitis B or C with histologic evidence of cirrhosis; active cigarette smoking or substance abuse; severe and untreated psychiatric illness; documented noncompliance with medical care; and absence of a reliable social network.

Relative contraindications, Dr. Angel said, include the clinical state at the moment of notification or referral, such as the presence of hemodynamic instability, excessive physical deterioration, or severe muscle atrophy that impedes performing outpatient rehabilitation. Also taken into account is the need for invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) support.

"Colonization by multiresistant or panresistant bacteria, fungus, or mycobacteria is another contraindication," Dr. Angel said, "as are other medical conditions such as coronary artery disease, liver and renal disease, gastroesophageal reflux, or symptomatic osteoporosis, and having a body mass index higher than 30 kg/m^2."

For each of the following indications for transplantation, the success rates vary according to the condition:

Candidacy for the procedure is now based on disease progression and chance of survival.

DR. ANGEL

► **COPD/emphysema.** In a select group of patients with COPD/emphysema, transplantation provides both survival and quality of life benefits.

Referral criteria include a BODE index of 7-10 points, or at least one of the following: a history of hospitalization for exacerbation associated with acute hypercapnia; pulmonary hypertension or cor pulmonale, or both, despite oxygen therapy; and an FEV_1 (forced expiratory volume in 1 second) of less than 20% and either a DLCO (diffusing capacity of the lungs for carbon monoxide) finding of less than 20% or homogeneous distribution of emphysema.

► **Pulmonary fibrosis.** "The natural history of the disease is more predictable, and there are major limitations in effective therapy for this diagnosis," said Dr. Angel of the department of pulmonary and critical care medicine at the university.

Referral criteria, he said, include histologic or radiographic evidence of interstitial pneumonia, and any of the following: a DLCO of less than 39% predicted; a 10% or greater decrement in forced vital capacity during 6 months of follow-up; a decrease in pulse oximetry less than 88% during a 6-minute walk test; honeycombing on high-resolution CT; or development of secondary pulmonary hypertension.

► **Cystic fibrosis.** Patients with this condition "can get the most significant benefit and prolonged survival with lung transplantation," Dr. Angel said. "Referrals are often delayed, as there is [a] high emotional aspect in the management of these patients and their families."

Referral criteria, he said, include an FEV_1 of less than 30% of predicted, or rapidly declining lung function if FEV_1 is greater than 30% of predicted, and/or any of the following: increasing oxygen requirements, hypercapnia, and pulmonary hypertension.

► **Idiopathic pulmonary arterial hypertension.** "This is one of the most difficult conditions [in which] to determine the right time for transplantation," Dr. Angel said. "Significant improvements with medical therapy and increased awareness of the disease have decreased the number of lung transplants for this indication." Referral criteria, he said, include persistent New York Heart Association class III or IV on maximal medical therapy; low or declining 6-minute walk test findings; failing therapy with intravenous epoprostenol or equivalent; a cardiac index of less than 2 L/min per square meter, or a right atrial pressure exceeding 15 mm Hg.

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

Lung Transplantation Beneficial in Select CF Patients

BY SUSAN LONDON
Elsevier Global Medical News

DENVER – "Lung transplantation for cystic fibrosis can be performed successfully, with survival benefit and quality of life benefit," Dr. Keith C. Meyer, FCCP, told attendees of the international conference of the American Thoracic Society.

The median survival of patients with cystic fibrosis (CF) has increased dramatically, from 0.5 years in 1940 to 37 years in 2006, according to data from the Cystic Fibrosis Foundation. "We see more and more adults in clinics with time, and actually about 47% of patients have now reached adulthood at age 18," he noted. "However, many of them have severe lung dysfunction by the time they reach adulthood."

When it comes to referring patients for transplantation, "you have to weigh things very carefully and make sure you are providing benefit to your patient," noted Dr. Meyer, codirector of the Adult Cystic Fibrosis Program at the University of Wisconsin Hospital and Clinics in Madison. That is, the risks of the disease must be compared with the risks of transplantation.

As for the timing of transplantation, patterns suggest that patients go through three disease phases: one during which they are too well for transplantation, one during which they experience a rapid decline in their condition, and one during which they are too ill. The middle phase "is where you want to catch them, a window of opportunity," he said.

Current guidelines recommend that referral for lung transplantation be based on the individual patient, the referring physician's estimation of survival and quality of life, and the patient's desire for information (J. Heart Lung Transplant. 2006;25:745-55).

The guidelines also outline criteria for referring patients to a transplant center and for placing them on the wait list for lung transplantation. The main trigger for referral, in addition to clinical events signaling rapid deterioration, is a forced expiratory volume in 1 second (FEV_1) that has dropped below 30% of that predicted or has declined rapidly. The triggers for listing are oxygen-dependent respiratory failure, hypercapnia, and pulmonary arterial hypertension.

"You have to evaluate your patient very well," Dr. Meyer noted. "We do a thorough psychosocial evaluation at our center, as well as our full cardiopulmonary evaluation. Other testing is done as required, and an infection-specific evaluation – we have all our patients hooked up with an infectious disease specialist before transplant."

Absolute contraindications to transplantation include things like untreatable advanced dysfunction in other organs, and documented noncompliance (J. Heart Lung Transplant. 2006;25:745-55). Relative contraindications include things like critical or unstable clinical condition, and colonization with highly resistant or virulent pathogens, although exceptions are sometimes made for patients with CF.

AMONG ALL LUNG TRANSPLANT RECIPIENTS WITH VARIOUS CONDITIONS, PATIENTS WITH CYSTIC FIBROSIS HAVE THE BEST SURVIVAL.

For example, "if they are colonized with *Aspergillus,* we still will do the transplantation," explained Dr. Meyer. "Of course, over half of our patients with CF *are* colonized with *Aspergillus*. We just want to make sure that there are not perhaps some other complications along with the *Aspergillus*."

The lung allocation score, adopted in 2005, "has changed things a little bit. We tend to transplant patients at the right time because we are better able to match them with donors," he said. Patients with CF and patients with idiopathic pulmonary fibrosis are given priority.

The lung allocation score "rises with disease progression," Dr. Meyer noted. The mean score for patients with CF who are candidates for lung transplantation is among the highest of all candidates for lung transplantation, at approximately 35 (Am. J. Transplant. 2006;6:1212-27).

"Bilateral lung transplant is the procedure of choice," he said. Adults with CF now make up a quarter of all adults undergoing bilateral lung transplantation (J. Heart Lung Transplant. 2010;29:1083-141). As of 2009, roughly 200 patients with CF were undergoing lung transplantation annually.

Among all lung transplant recipients with various conditions, patients with CF have the best survival (J. Heart Lung Transplant. 2010;29:1083-141). This is "probably partially due to the fact that they are younger and maybe because with all this tremendous pulmonary inflammation they had over time, maybe their immune rejection response is somewhat blunted."

A total of 72 patients with CF have undergone lung transplantation at his center, and their 10-year survival rate is 67%.

"Things are often rocky in the first few months. If they can make it out to 1 year and things are going pretty well, they tend to do well over time," he said.

Dr. Meyer reported having no conflicts of interest related to his presentation. ■

Steroids May Help if Given Early

ALI-ARDS • *from page 1*

did regular infection surveillance with regular bronchoscopies, and they avoided the use of neuromuscular blockers," said Dr. Pastores, who is also a professor of medicine and anesthesiology at Cornell University in New York.

The researchers found that patients in the treatment arm had a greater than 1-point drop in their lung injury score. They also found no significant increase in complications such as infection, "and because they avoided neuromuscular blockers, there was hardly any incidence of neuromuscular weakness or neuropathy," Dr. Pastores said.

In a subsequent review of five trials on the use of steroids for the treatment of ARDS that enrolled a total of 518 patients, Dr. Pastores and his associates observed that the steroid dosing and treatment duration were different across the trials, and that infection surveillance was not done routinely (Intensive Care Med. 2008;34:61-9). However, three of the trials in which patients received steroids before day 14 of ARDS found a slight benefit, with a number needed to treat of six.

"If you look at the patients who were randomized to the methylprednisolone arm, the mortality rate was 24%, which is about 16% less than the control arm," Dr. Pastores said of the 245 patients in these three trials. "From this review, we concluded that prolonged glucocorticoid treatment substantially and significantly improves meaningful patient-centered outcomes in terms of less ventilator days, less days in the ICU, and perhaps a distinct survival benefit – only in patients who have steroids early in the course of acute lung injury, however."

A more recent systematic review that factored in additional trials concluded that prolonged glucocorticoid treatment has a "distinct survival benefit" when initiated before day 14 of ARDS, with a number needed to treat of four (Crit. Care Med. 2009;37:1594-603). No significant differences in the rate of neuromyopathy or other major events were seen between the treatment and control groups.

"However, we have to be cautious," Dr. Pastores said of the findings. "There are limitations in all of the systematic reviews on this topic. There are marked differences in study designs, patient characteristics, doses of steroids, dosing strategies, and duration of therapy."

In 2008, a task force convened by the American College of Critical Care Medicine concluded that moderate-dose glucocorticoids should be considered in patients with early severe ARDS (PaO_2/FiO_2 of less than 200) and before day 14 in patients with unresolving ARDS (Crit. Care Med. 2008;36:1937-49). "We could not come to a definitive conclusion or recommendation on patients with less severe ALI," said Dr. Pastores, who was a member of the task force. "Keep in mind that the recommendation is based on level 2B evidence for a mortality benefit. It's a weak recommendation because the quality of the evidence was moderate; it wasn't very strong because we didn't have enough good randomized, controlled trials. For reduction in duration of mechanical ventilation, however, the evidence is strong (1B), with the aggregate of data showing a doubling of extubation, in comparison to controls, by days 7 and 14."

He noted that physicians should give steroids in conjunction with infection surveillance, "avoiding neuromuscular blockers if you can, and being concerned about the phenomenon of rebound inflammation if you stop steroids abruptly."

Inhaled nitric oxide has also been studied in ALI/ARDS. A Cochrane review of 13 randomized, controlled trials involving 1,303 patients found no significant effect with this approach in overall mortality, but did show a transient improvement in oxygenation in the first 24 hours. The review also found that inhaled nitric oxide had no significant effect on duration of ventilation, ventilator-free days, and ICU and hospital length of stay. An increased risk of renal impairment among adults was also noted (Cochrane Database Syst. Rev. 2010 Oct. 23 [doi:10.1002/14651858.CD002787.pub2]).

"The conclusion from this meta-analysis was that there was no mortality benefit, and in fact [nitric oxide] might even be harmful," Dr. Pastores said.

Intriguing findings on the use of neuromuscular blockers in severe, early ARDS were presented in 2010 after a multicenter trial of 340 patients who were randomized to IV cisatracurium infusion or placebo for 48 hours (N. Engl. J. Med. 2010;363:1107-16). The primary outcomes were 90-day mortality and ventilator-free days.

Patients in the treatment group had lower 90-day mortality and more ventilator-free days, compared with those in the placebo group.

"Neuromuscular blockers may facilitate lung-protective ventilation in this patient population by improving patient-ventilator synchrony," Dr. Pastores said. "They may also improve chest wall compliance and reduce oxygen consumption, and possibly cause a decrease in lung or systemic inflammation."

The study's limitations were that "it only involved cisatracurium and therefore may not apply to other neuromuscular blockers. There were also no data on conditions known to antagonize or potentiate neuromuscular blockers," he added.

Another treatment strategy for ALI/ARDS – the routine use of aerosolized $beta_2$-agonists – cannot be recommended at this time because of the results of a recent trial in which patients were randomized to 5 mg aerosolized albuterol or saline placebo every 4 hours for up to 10 days. The primary outcome was ventilator-free days. "The trial had to be stopped for futility because there was no improvement in ventilator-free days," Dr. Pastores said.

"In fact, there was a suggestion of a slight trend of increasing morbidity among patients in the treatment group.

Steroid treatment significantly improves outcomes, but only when given early in the course of ALI.

DR. PASTORES

The investigators theorized that the lung-protective ventilation and conservative fluid management reduced lung injury and water to the extent that additional lung fluid clearance with $beta_2$-agonists had no additional beneficial effect," he said.

The role of pharmaconutrition has also been studied in this patient population. According to Dr. Pastores, three previous trials of continuous omega-3 enteral feeds showed improved PaO_2/FiO_2 ratio, shorter ventilator time and ICU stay, and fewer organ failures and lower mortality. However, a more recent randomized, controlled trial of 272 adults found that twice-daily administration of omega-3 fatty acids plus antioxidant supplementation did not improve ventilator-free days or other clinical outcomes (JAMA 2011;306:1574-81). "There was some suggestion that perhaps it was harmful to these patients," Dr. Pastores said. For example, 60-day hospital mortality was higher among the patients in the treatment group, compared with those in the placebo group (27% vs. 16%, respectively; $P = .054$).

Future nonventilatory therapies that might hold promise for patients with ALI/ARDS, he said, include inhaled protein C, tissue factor inhibition, statins, and the extended use of steroids in severe community-acquired pneumonia.

Dr. Pastores disclosed that he has received grant support from Altor Bioscience Corp. and from Spectral Diagnostics Inc. ■

Long-Term Impairments Common in ALI/ARDS

'The pace of recovery is protracted and likely incomplete in the current paradigm of care.'

BY DOUG BRUNK
Elsevier Global Medical News

HONOLULU – Although large numbers of patients are surviving acute lung injury/adult respiratory distress syndrome, long-term impairments are common and "striking for their relationship to neuropsychiatric dysfunction," Dr. Jesse Hall, FCCP, said at CHEST 2011, the annual meeting of the American College of Chest Physicians.

"The pace of recovery is protracted and likely incomplete in the current paradigm of care," said Dr. Hall, professor of medicine, anesthesia, and critical care at the University of Chicago. "Interventions including those begun at the onset of critical illness will hopefully improve these outcomes."

According to the best epidemiologic study on the topic, an estimated 191,000 cases of acute lung injury (ALI) and 141,500 cases of adult respiratory distress syndrome (ARDS) occur each year in the United States, causing a combined 133,500 deaths annually (N. Engl. J. Med 2005;353:1685-93). Implementation of low-tidal-volume ventilation over the past decade has led to an improvement in survival among this patient population, Dr. Hall said, but "we are just beginning to understand through descriptive studies what the path is for these patients down the road. We really lack many prospective trials in that arena."

One study of 109 ARDS patients who were followed for 1 year found that most developed a restrictive lung lesion that improved in the first 6-12 months (N. Engl. J. Med 2003;348:683-93). "The most consistent pulmonary function test abnormality tends to be low diffusion capacity that often resolves over time," Dr. Hall said. Some of their general functional limitation correlates to their pulmonary dysfunction, "but much of it does not," he said. "In fact, it's not what the patients report. They start to have a very low functional status 6, 12, and more months out, and they don't ascribe it primarily to their lung dysfunction."

Residual areas of fibrosis are not unusual on follow-up CT scans of ALI/ARDS patients, and many of these patients develop airway abnormalities such as bronchiectasis associated with their lung injury, said Dr. Hall, who is also section chief of pulmonary and critical care medicine at the University of Chicago.

The 2003 study of 109 ARDS patients found that all subjects reported poor function due to loss of muscle bulk, proximal weakness, and fatigue. Some (12%) reported persistent pain at the chest tube site, 7% reported entrapment neuropathies, 7% had tracheotomy site problems, 5% had large joint enlargement/immobility from heterotopic ossification, and 4% had immobility in the form of contracted fingers or frozen shoulders. "It can be up to a year before patients regain their body weight after this episode," Dr. Hall said.

Neuromuscular sequelae may include myopathy, peripheral neuropathy, or deconditioning. "Any given patient can have any combination of those," he said. "Some of these disorders are reasonably strongly associated with some of our therapies. Most of our patients have a combination of peripheral neuropathies and myopathies that may by themselves be modest but are attended by extreme deconditioning. The neuromuscular sequelae of critical illness are variable in terms of recovery over months and years, and some patients seem to never fully recover."

The impact of neuropsychiatric sequelae can be significant. One study of 55 ARDS patients found that 100% had cognitive and affective impairments at hospital discharge, and 30% had generalized cognitive decline 1 year later (Am. J. Respir. Crit. Care Med. 1999;160:50-6). In the 2003 study, only 49% of the ARDS patients who had been employed were back to work at 1 year. "This is an astounding economic and financial consequence for the patient and the family," Dr. Hall commented. "Scores on the Short Form-36 were below normal in all eight domains at 3-, 6-, and 12-month follow-up from ICU discharge. There were improvements in most SF-36 categories, but almost none were back to normal."

'There were improvements in most SF-36 categories, but almost none were back to normal.'

DR. HALL

Dr. Hall said that changes in the current health care system are needed to improve outcomes for ALI/ARDS patients. Currently, "it's difficult for those in our discipline to figure out how to become a change agent, or help our patients acquire what they need to optimize their recovery," he explained. "It's not likely, in fact, to be done by critical care doctors down the road."

One study from the United Kingdom sought to determine if giving patients a self-help rehabilitation manual would affect their general functional status "and therefore their psychiatric axes as well, and maybe even make them more functional," Dr. Hall said. For the study, patients in the control group received ward visits, three telephone calls at home, and clinic appointments at 8 weeks and 6 months, whereas patients in the intervention group received the same plus a 6-week self-help rehabilitation manual. At the end of 6 weeks, patients in the intervention group had significantly better physical function scores, compared with controls (Crit. Care Med. 2003;31:2456-61). Unfortunately, such benefits were not seen in another recent prospective trial.

In a recent trial conducted by a group of researchers that included Dr. Hall, 104 critical care patients who required ventilation were randomized to either early physical and occupational therapy during periods of daily interruption of sedation, or to daily interruption of sedation with therapy as ordered by the primary care team (Lancet 2009; 373:1874-82). Compared with controls, patients who received early physical and occupational therapy had better return to independent functional status at hospital discharge (59% vs. 35%, respectively) and less ICU delirium (2 days vs. 4 days).

Dr. Hall concluded by noting that the brain and the neurologic and musculoskeletal systems "are likely the last to recover after ALI/ARDS, and may not recover fully to the status patients had before. We don't know what matters most for long-term recovery. It's reasonable to think that shortening ICU and mechanical ventilation time would be beneficial."

Dr. Hall disclosed that he receives honoraria from the American College of Chest Physicians and the American Thoracic Society. ■

Adverse Effects Discourage Imatinib for Treatment of SSc

BY LUIS MAZARIEGOS
Elsevier Global Medical News

Treatment for systemic sclerosis–associated active interstitial lung disease with a relatively high dose of imatinib can be effective, but it carries many side effects, judging from findings of a 20-person study.

VITALS

Major Finding: Five of the 20 patients treated with imatinib discontinued treatment due to adverse side effects. Improvements of 1.74% in the estimated FVC % predicted, 4.17% in the TLC % predicted, and 1.46% in the DLCO % predicted were seen over a 1-year period.

Data Source: The study was conducted on 20 SSc patients at two scleroderma centers in the United States.

Disclosures: The researchers reported no relevant financial disclosures. Novartis Pharmaceuticals provided the study drug and partial support for the study.

The study subjects met the American College of Rheumatology criteria for systemic sclerosis (SSc). The mean disease duration was less than 10 years, their mean forced vital capacity (FVC) was less than 85% of predicted, their dyspnea on exertion was at least grade 2 on the magnitude of task component of the Mahler Baseline Dyspnea Index, and high-resolution computed tomography showed the presence of ground-glass opacifications.

Patients with SSc received oral therapy with imatinib up to 600 mg/day for a period of 1 year. The researchers recorded adverse events and tested pulmonary function. In addition, the modified Rodnan skin thickness score (MRSS) was assessed every 3 months, according to Dr. Dinesh Khanna of the University of California at Los Angeles.

Imatinib treatment increased FVC by 1.74%, though this was not statistically significant. In addition, the MRSS increased by 3.9 units. The total lung capacity increased by 4.17% over predicted and the diffusing capacity for carbon monoxide improved by 1.46% versus predicted, according to the investigators (Arthritis Rheum. 2011;63: 3540-6). Of the 20 who participated, 5 did not complete the study due to adverse events that were caused by the treatment itself. A further two dropped out due to adverse events caused by SSc, and one was lost due to follow-up. The rest completed the study.

Some of the common adverse events the participants experienced were fatigue, edema of the face and/or lower extremities, nausea and vomiting, diarrhea, generalized rash, and new-onset proteinuria.

Because of its efficacy, the authors suggest further research with smaller doses of imatinib, so as to reduce adverse effects while maintaining the positive effects. ■

COMMENTARY

Dr. Jeana O'Brien, FCCP, comments: This small study regarding treatment with imatinib in patients with systemic sclerosis–associated interstitial lung disease (ILD) revealed no significant improvements in objective pulmonary function and only very modest gains on the Mahler dyspnea index. This dose of imatinib unfortunately also produced significant adverse effects resulting in a high discontinuation rate. While additional study with lower doses of the medication may show fewer adverse effects – and is reasonable to perform given the limited therapeutic options – these results cast doubt as to the overall ultimate benefit of imatinib for SSc-associated ILD.

‘C for Compressions’ Usurps ‘A for Airway’

BY SHERRY BOSCHERT
Elsevier Global Medical News

SAN FRANCISCO – The alphabet is changing for critical care of patients in cardiac arrest.

“A is for airway” is no longer at the top of the list. The ABCs (airway, breathing, and circulation) of cardiopulmonary resuscitation have been replaced by an emphasis on CAB – compressions, airway, and breathing, in that order.

The American Heart Association promotes the “CPR is as easy as C-A-B” slogan, and the key to success in treating cardiac arrest is high-quality, uninterrupted chest compressions, Dr. Robert J. Vissers said at the annual meeting of the American College of Emergency Physicians.

“Airway may not always come first” if the patient has lost perfusion and circulation, said Dr. Vissers, chief of emergency medicine at Legacy Emanuel Medical Center, Portland, Ore. “It’s hard for me to say, because I’m an airway guy.”

While “C” stands for compressions, it also serves to remind physicians to attend to cardioversion, capnography, cooling, and catheterization, if needed. Dr. Vissers addressed each of these in more detail.

“These are the things that recently have led to pretty substantial improvements in the outcomes of these patients,” he said.

Compressions. With high-quality, uninterrupted chest compressions, the patient gets good passive ventilation, which may be superior to positive pressure ventilation in these situations. Aim for 30 compressions per breath. Consider creating a supraglottic airway without interrupting the CPR, he said.

Put some muscle into it to maintain compressions 2 inches in depth with full recoil, at a rate of 100 compressions per minute. If more than one person is available, take turns applying compressions to reduce fatigue. Monitor the patient closely with end-tidal capnography. (See below.)

Proper compressions restore cerebral and coronary perfusion. Sustained coronary perfusion pressure is critical to successful defibrillation.

Cardioversion. The first 4 minutes after cardiac arrest provide the greatest chance of successful cardioversion (defibrillation). If more than 4 minutes have elapsed, reperfuse the myocardium with a few minutes of chest compressions before applying shock. Wait 2 minutes after defibrillation to check the pulse, and maintain compressions during that time.

The traditional admonition to “clear!” before shocking may not be necessary, Dr. Vissers said. Studies have shown that no appreciable electrical current reaches the people applying compressions if they are wearing gloves and a biphasic defibrillator is used for cardioversion.

Capnography. Confirm proper tube placement for capnography, which helps assess the quality of the CPR and identify return of spontaneous circulation without checking pulses. Capnography readings also help predict outcome.

“I think capnography is one of the most underutilized tools that we have for the critically ill patient,” Dr. Vissers said.

‘C’ ALSO SERVES TO REMIND PHYSICIANS TO ATTEND TO CARDIOVERSION, CAPNOGRAPHY, COOLING, AND CATHETERIZATION.

High-quality compressions and coronary perfusion pressures correlate with end-tidal carbon dioxide ($ETCO_2$) levels of 20-25 mm Hg on capnography. A sudden rise in $ETCO_2$ suggests return of spontaneous circulation and is more sensitive than manual pulse checks. If $ETCO_2$ readings persistently stay below 10 mm Hg, return of spontaneous circulation is unlikely. In studies, an $ETCO_2$ less than 10 mm Hg after 20 minutes of compressions was associated with zero chance of return of spontaneous circulation.

Cooling. For unconscious adults who went into cardiac arrest outside of hospital care, cooling the body to 32-34° C for 12-24 hours improves chances of a good outcome, Dr. Vissers said. Applying ice packs to the groin, axilla, and neck will cool the body about 0.2-1° C per hour. The best cooling method may be cooling blankets that circulate cooled water through material designed to promote heat exchange. The blankets cool a body on average by 1-1.5° C per hour.

Used in combination, the ice packs can be removed when the body temperature reaches 33° C and the blankets left on to maintain the cool temperature for 12-24 hours. “That works very well,” he said. Cooled normal saline infusions or cooling catheters also are options for cooling a body after cardiac arrest.

Of every 4-13 patients cooled after cardiac arrest, 1 will leave the hospital neurologically intact, he said.

Catheterization. Early percutaneous coronary intervention benefits patients with cardiac arrest, even those without ST-segment elevation MI, studies suggest. Consider transferring the patient for cardiac catheterization. It’s okay to cool the body and then transfer for catheterization. This may become a more common model as care after cardiac arrest becomes more regionalized, he said.

Dr. Vissers said he has no relevant conflicts of interest. ■

Most Smokers Want to Quit, but Few Get Help

BY PATRICE WENDLING
Elsevier Global Medical News

Most smokers in the United States want to quit, but when they try, they do so without medications or formal counseling from health professionals, according to a new study by the Centers for Disease Control and Prevention.

In 2010, 69% of adult cigarette smokers said they wanted to quit, and 52.4% had recently tried to do so for more than 1 day.

Still, 68.3% of current smokers who tried to quit did so without using evidence-based cessation counseling or medications, and fewer than half (48.3%) of those who saw a health professional in the past year reported receiving advice to quit (MMWR 2011 Nov. 11;60:1513-9).

“What this means is that there’s significant room for improvement in this arena because use of these treatments can double or triple success rates,” Dr. Tim McAfee, director of the Office of Smoking and Health, said during a press briefing on the report.

Among those who visited a health care provider, women (51.7%) were more likely than men were (44.8%) to have received a health professional’s advice to quit. More than half of those aged 65 years and older (57%) received such advice.

Among the various racial groups, Hispanics were the least likely to have received advice, at 34.7%, compared with 50% of whites and 46% of blacks, according to the study, which was based on 2001-2010 National Health Interview Survey data.

When asked by reporters how the overall 48% counseling rate stacks up with previous years, Dr. McAfee said it’s lower than in their previous surveys, but added that the current survey had changed and that an earlier question on tobacco use had been removed.

“We’re not sure if this is a real trend or an artifact in the way the survey questions were administered,” he said.

Ann Malarcher, Ph.D., lead author of the study, said other national data sets that examine whether smokers receive advice to quit are showing no change over time. Those data sets show counseling rates as high as 60%.

One of the more troubling findings in the report is that non-Hispanic blacks had the highest level of interest in quitting and the most quit attempts in the past year, but also the lowest rate of successfully quitting, at 3.3% vs. 6.0% for whites and 9.5% for Hispanics.

One possible explanation for the lower success rate is that blacks were less likely to use counseling and/or medication than were whites (21.6% vs. 36.1%). In addition, blacks are three times more likely than whites were to smoke menthol cigarettes (76.7% vs. 23.6%), which has been found to reduce the likelihood of quitting, Dr. McAfee said.

The report, which was released 1 week ahead of the Great American Smokeout set for Nov. 17, also found marked differences in successful smoking cessation by education level and insurance status. Just 3.2% of smokers with less than a high school education quit smoking, compared with 11.4% of those with a college degree. Notably, 7.8% of those with private insurance reported quitting, compared with 4.6% receiving Medicaid, 5.5% with Medicare, and 9.3% in the military.

One encouraging piece of news in the report is that there has been an annual increase in quit attempts over the last 10 years for smokers aged 25-64 years, Dr. McAfee said. During the same period, quit attempts remained stable among younger smokers, aged 18-24 years, and those aged 65 years and older.

Overall, 6.2% of smokers reported stopping smoking. It’s hard to say how this compares with previous years because other surveys didn’t typically ask this, although it is a new measure required for the Healthy People 2020 objective, Dr. Malarcher said.

“Why we added that measure for these objectives is that we really want to look at recent success,” she said. “We hope to move the needle and get more people to quit each year.”

“Of those who made a quit attempt, just under one-third received counseling and medication,” Dr. McAfee said.

He acknowledged the controversy over the use of varenicline (Chantix) and advised smokers to ask their physician. He added that the smoking-cessation drug is effective and that data on the reported neuropsychiatric effects are mixed. Notably, a study reported last week that varenicline was eight times more likely to be linked with suicidal behavior or depression than were other nicotine replacement products (PLoS One 2011 Nov. 2; [doi:10.1371/journal.pone.0027016]), while two recent Food and Drug Administration–sponsored studies found no relationship between varenicline use and the risk of psychiatric hospitalization.

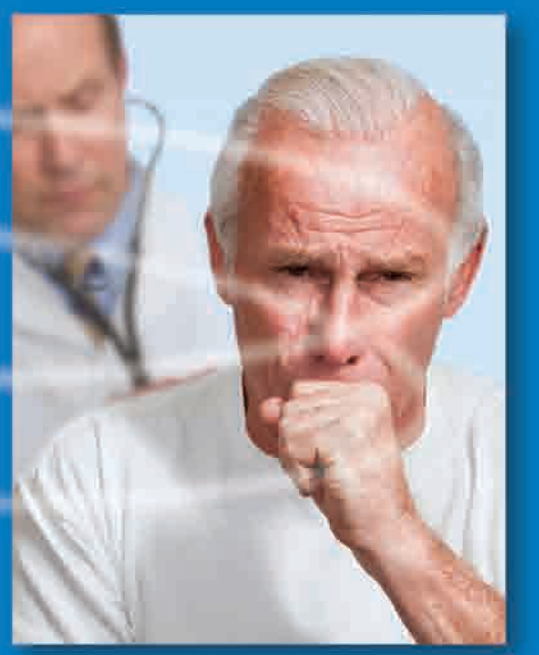
Finally, Dr. McAfee said the study is somewhat reassuring in that it shows that the 45.3 million Americans (19.3%) who still smoke are as interested in quitting as they were 10 years ago. “What we’re concerned about, honestly, is that society has been losing its enthusiasm for supporting smokers” in their quit attempts, he said. “We’ve seen a degradation in funding by the states over the last 3 years that is deeply concerning, especially considering the increasing amount of money they are bringing in through taxes and the [Tobacco] Master Settlement.” ■

For patients with severe COPD associated with chronic bronchitis and a history of exacerbations

COPD EXACERBATIONS

are serious events...

Reducing Patient Risk Is Critical



INDICATIONS AND USAGE

DALIRESP is indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. DALIRESP is not a bronchodilator and is not indicated for the relief of acute bronchospasm.

Please see Important Safety Information and Brief Summary of full Prescribing Information on the following pages and at www.DALIRESP.com.

COPD=chronic obstructive pulmonary disease.

Daliresp®
(roflumilast) tablets
500 mcg

IMPORTANT SAFETY INFORMATION

Contraindications

DALIRESP is contraindicated in patients with moderate to severe liver impairment (Child-Pugh B or C).

Warnings and Precautions

- DALIRESP is not a bronchodilator and should not be used for the relief of acute bronchospasm.
- Prescribers should advise patients, their caregivers, and families to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if such changes occur, to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment if such events occur. Before using DALIRESP in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with DALIRESP.
  - Treatment with DALIRESP is associated with an increase in psychiatric adverse reactions. In controlled clinical trials 5.9% of patients treated with DALIRESP reported psychiatric adverse reactions vs 3.3% treated with placebo. The most common psychiatric adverse reactions were insomnia (2.4% vs 1.0%), anxiety (1.4% vs 0.9%), and depression (1.2% vs 0.9%).
  - Three patients treated with DALIRESP experienced suicide-related adverse reactions (one completed suicide and two suicide attempts) compared to one patient (suicidal ideation) treated with placebo.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the following pages and at www.DALIRESP.com.

For patients with severe COPD associated with chronic bronchitis and a history of exacerbations

TREAT NOW WITH DALIRESP®

The first and only selective PDE4 inhibitor to reduce the risk of COPD exacerbations[1,2]

- Reduces moderate or severe exacerbations by 17% vs placebo[1,3,4]
- Effective alone or in combination with a bronchodilator[1,3]
- Effective in older and younger patients (>65 and 40-65 years)[1,3]
- Statistically significant increase in lung function (pre-bronchodilator FEV_1) of 48 mL vs placebo[1,4]
  - DALIRESP is not a bronchodilator; this increase was not clinically significant[1,3]
- The first class of drugs approved for COPD in 25 years[2,5]

ONCE-DAILY
ORAL

Tablet shown not actual size.

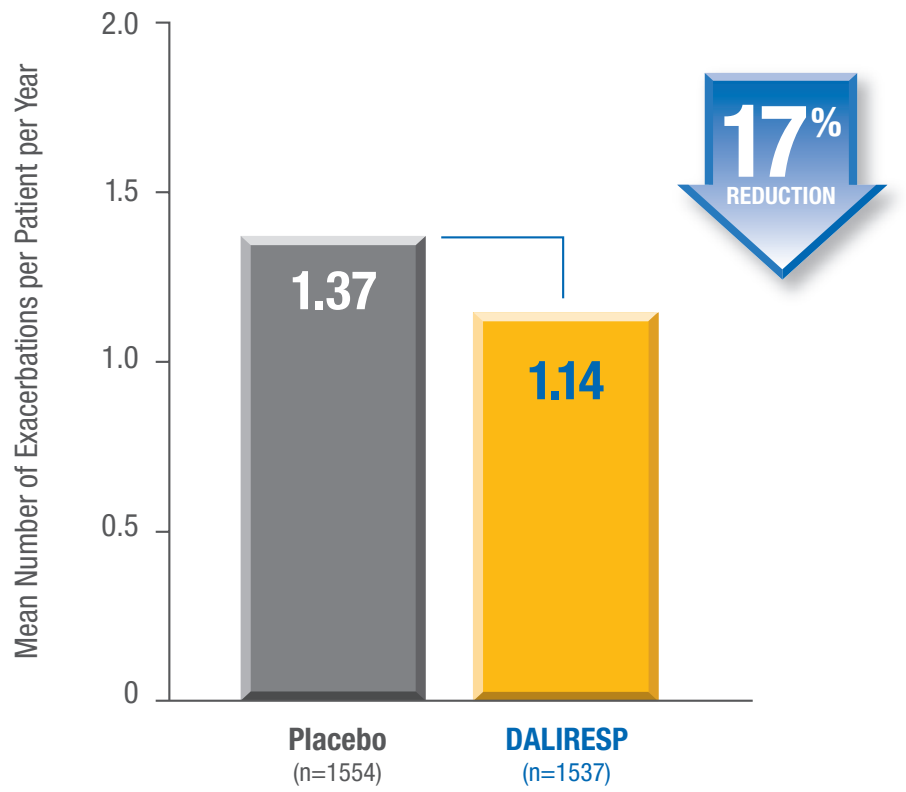
- Patients should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated and treatment discontinuation considered.
  - In addition to weight loss being reported as a common adverse reaction (7.5% of patients treated with DALIRESP vs 2.1% placebo), weight was prospectively assessed in two 1-year clinical trials. In these studies that compared DALIRESP to placebo, 20% vs 7% experienced moderate weight loss (5-10% of body weight) and 7% vs 2% experienced severe weight loss (>10% body weight).
  - During the follow-up period after discontinuing DALIRESP, the majority of patients regained some of the weight they had lost.
- Use with strong cytochrome P450 enzyme inducers (eg, rifampicin, phenobarbital, carbamazepine, phenytoin) is not recommended, as they decrease the exposure and may reduce the therapeutic effectiveness of DALIRESP.

Daliresp®
(roflumilast) tablets
500 mcg

For patients with severe COPD associated with chronic bronchitis and a history of exacerbations

DALIRESP significantly reduces exacerbations

REDUCTION IN THE RATE OF MODERATE OR SEVERE EXACERBATIONS[3,4]



P=0.0003 vs placebo

Study design: A pre-specified pooled analysis from 2 identical, 52-week, double-blind, placebo-controlled trials in patients with severe COPD associated with chronic bronchitis and a history of exacerbations (N=3091). Median patient age was 64 years; 76% male, 84% Caucasian. LABAs or short-acting anticholinergics were allowed as concomitant treatment. The reduction in the rate of moderate (requiring treatment with systemic glucocorticosteroids) or severe (resulting in hospitalization and/or leading to death) exacerbations and change in lung function (pre-bronchodilator FEV_1) were co-primary endpoints. Each study met both co-primary endpoints.

- Moderate exacerbations were defined as those requiring treatment with systemic corticosteroids[1]
- Severe exacerbations were defined as resulting in hospitalization and/or death[1]

INDICATIONS AND USAGE

DALIRESP is indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. DALIRESP is not a bronchodilator and is not indicated for the relief of acute bronchospasm.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- Prescribers should advise patients, their caregivers, and families to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if such changes occur, to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment if such events occur. Before using DALIRESP in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with DALIRESP.

References: 1. DALIRESP (roflumilast) Prescribing Information. Forest Pharmaceuticals, Inc. St. Louis, MO. **2.** US Food and Drug Administration. FDA approves new drug to treat chronic obstructive pulmonary disease. March 1, 2011. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm244989.htm. Accessed October 19, 2011. **3.** Data on file. Forest Laboratories, Inc. **4.** Calverley PMA, Rabe KF, Goehring U-M, Kristiansen S, Fabbri LM, Martinez FJ; for the M2-124 and M2-125 study groups. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet.* 2009;374:685-694. **5.** US Food and Drug Administration. Atrovent approval history (NDA 019085, 1986). Drugs@FDA. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed October 19, 2011.

For patients with severe COPD associated with chronic bronchitis and a history of exacerbations

Effective with LABAs or short-acting anticholinergics

In the same studies:

DALIRESP significantly reduced the rate of exacerbations vs placebo in patients using a bronchodilator[1,3]

CONSISTENT EFFECT WITH A CONCOMITANT BRONCHODILATOR[1,3]

DALIRESP with LABAs (Long-acting $ß_2$ Agonists)	✓
DALIRESP with Short-acting Anticholinergics	✓

Study design: A pre-specified pooled analysis from 2 identical, 52-week, double-blind, placebo-controlled trials in patients with severe COPD associated with chronic bronchitis and a history of exacerbations (N=3091). Median patient age was 64 years; 76% male, 84% Caucasian. LABAs and short-acting anticholinergics were allowed and were used by 44% and 35% of patients treated with DALIRESP and 45% and 37% of patients treated with placebo, respectively. The reduction in the rate of moderate (requiring treatment with systemic glucocorticosteroids) or severe (resulting in hospitalization and/or leading to death) exacerbations and change in lung function (pre-bronchodilator FEV_1) were co-primary endpoints. Each study met both co-primary endpoints.

- **The effect with concomitant LABAs or short-acting anticholinergics was similar to that seen in the overall population[1,3]**

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- Patients should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated and treatment discontinuation considered.

Adverse Reactions

In clinical trials the most common adverse reactions (≥2% and greater than placebo) were diarrhea (9.5% vs 2.7%), weight loss (7.5% vs 2.1%), nausea (4.7% vs 1.4%), headache (4.4% vs 2.1%), back pain (3.2% vs 2.2%), influenza (2.8% vs 2.7%), insomnia (2.4% vs 1.0%), dizziness (2.1% vs 1.1%), and decreased appetite (2.1% vs 0.4%).

Please see additional Important Safety Information on the previous pages and Brief Summary of full Prescribing Information on the following page and at www.DALIRESP.com.

Forest Pharmaceuticals, Inc.
Subsidiary of Forest Laboratories, Inc.
St. Louis, Missouri 63045

Daliresp®
(roflumilast) tablets
500 mcg

 84-12000308T 11/11

DALIRESP™ (roflumilast) tablets **Rx Only**
Brief Summary of full Prescribing Information
Initial U.S. Approval: 2011

INDICATIONS AND USAGE

DALIRESP™ is indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.

Limitations of Use

DALIRESP is not a bronchodilator and is not indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS

The use of DALIRESP is contraindicated in the following conditions:

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

WARNINGS AND PRECAUTIONS

Treatment of Acute Bronchospasm

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

Psychiatric Events including Suicidality

Treatment with DALIRESP is associated with an increase in psychiatric adverse reactions. In 8 controlled clinical trials 5.9% (263) of patients treated with DALIRESP 500 mcg daily reported psychiatric adverse reactions compared to 3.3% (137) treated with placebo. The most commonly reported psychiatric adverse reactions were insomnia, anxiety, and depression which were reported at higher rates in those treated with DALIRESP 500 mcg daily (2.4%, 1.4%, and 1.2% for DALIRESP versus 1.0%, 0.9%, and 0.9% for placebo, respectively) *[see Adverse Reactions (6.1)]*. Instances of suicidal ideation and behavior, including completed suicide, have been observed in clinical trials. Three patients experienced suicide-related adverse reactions (one completed suicide and two suicide attempts) while receiving DALIRESP compared to one patient (suicidal ideation) who received placebo.

Before using DALIRESP in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with DALIRESP in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with DALIRESP if such events occur.

Weight Decrease

Weight loss was a common adverse reaction in DALIRESP clinical trials and was reported in 7.5% (331) of patients treated with DALIRESP 500 mcg once daily compared to 2.1% (89) treated with placebo [*see Adverse Reactions (6.1)*]. In addition to being reported as adverse reactions, weight was prospectively assessed in two placebo-controlled clinical trials of one year duration. In these studies, 20% of patients receiving roflumilast experienced moderate weight loss (defined as between 5-10% of body weight) compared to 7% of patients who received placebo. In addition, 7% of patients who received roflumilast compared to 2% of patients receiving placebo experienced severe (>10% body weight) weight loss. During follow-up after treatment discontinuation, the majority of patients with weight loss regained some of the weight they had lost while receiving DALIRESP. Patients treated with DALIRESP should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of DALIRESP should be considered.

Drug Interactions

A major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP3A4 and CYP1A2. The administration of the cytochrome P450 enzyme inducer rifampicin resulted in a reduction in exposure, which may result in a decrease in the therapeutic effectiveness of DALIRESP. Therefore, the use of strong cytochrome P450 enzyme inducers (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin) with DALIRESP is not recommended. [*see Drugs That Induce Cytochrome P450 (CYP) Enzymes (7.1) and Clinical Pharmacology (12.3)*].

ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

- Psychiatric Events Including Suicidality *[see Warnings and Precautions (5.2)]*
- Weight Decrease *[see Warnings and Precautions (5.3)]*

Adverse Reactions in Clinical Studies

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

The safety data described below reflect exposure of 4438 patients to DALIRESP 500 mcg once daily in four 1-year placebo-controlled trials, two 6-month placebo-controlled trials, and two 6-month drug add-on trials *[see Clinical Studies (14.1)]*. In these trials, 3136 and 1232 COPD patients were exposed to DALIRESP 500 mcg once daily for 6 months and 1-year, respectively.

The population had a median age of 64 years (range 40-91), 73% were male, 92.9% were Caucasian, and had COPD with a mean pre-bronchodilator forced expiratory volume in one second (FEV_1) of 8.9 to 89.1% predicted. In these trials, 68.5% of the patients treated with DALIRESP reported an adverse reaction compared with 65.3% treated with placebo.

The proportion of patients who discontinued treatment due to adverse reaction was 14.8% for DALIRESP-treated patients and 9.9% for placebo-treated patients. The most common adverse reactions that led to discontinuation of DALIRESP were diarrhea (2.4%) and nausea (1.6%).

Serious adverse reactions, whether considered drug-related or not by the investigators, which occurred more frequently in DALIRESP-treated patients include diarrhea, atrial fibrillation, lung cancer, prostate cancer, acute pancreatitis, and acute renal failure.

Table 1 summarizes the adverse reactions reported by ≥ 2% of patients in the DALIRESP group in 8 controlled COPD clinical trials.

Table 1: Adverse Reactions Reported by ≥ 2% of Patients Treated with DALIRESP 500 mcg daily and Greater Than Placebo

	Treatment	
Adverse Reactions (Preferred Term)	**DALIRESP** (**N=**4438) n (%)	**Placebo** (**N=**4192) n (%)
Diarrhea	420 (9.5)	113 (2.7)
Weight decreased	331 (7.5)	89 (2.1)
Nausea	209 (4.7)	60 (1.4)
Headache	195 (4.4)	87 (2.1)
Back pain	142 (3.2)	92 (2.2)
Influenza	124 (2.8)	112 (2.7)
Insomnia	105 (2.4)	41 (1.0)
Dizziness	92 (2.1)	45 (1.1)
Decreased appetite	91 (2.1)	15 (0.4)

Adverse reactions that occurred in the DALIRESP group at a frequency of 1 to 2% where rates exceeded that in the placebo group include:

Gastrointestinal disorders - abdominal pain, dyspepsia, gastritis, vomiting

Infections and infestations - rhinitis, sinusitis, urinary tract infection,

Musculoskeletal and connective tissue disorders - muscle spasms

Nervous system disorders - tremor

Psychiatric disorders - anxiety, depression

DRUG INTERACTIONS

A major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP3A4 and CYP1A2 [*see Clinical Pharmacology (12.3)*].

Drugs That Induce Cytochrome P450 (CYP) Enzymes

Strong cytochrome P450 enzyme inducers decrease systemic exposure to roflumilast and may reduce the therapeutic effectiveness of DALIRESP. Therefore the use of strong cytochrome P450 inducers (e.g., rifampicin, phenobarbital, carbamazepine, and phenytoin) with DALIRESP is not recommended *[see Drug Interactions (5.4) and Clinical Pharmacology (12.3)]*.

Drugs That Inhibit Cytochrome P450 (CYP) Enzymes

The co-administration of DALIRESP (500 mcg) with CYP3A4 inhibitors or dual inhibitors that inhibit both CYP3A4 and CYP1A2 simultaneously (e.g., erythromycin, ketoconazole, fluvoxamine, enoxacin, cimetidine) may increase roflumilast systemic exposure and may result in increased adverse reactions. The risk of such concurrent use should be weighed carefully against benefit. *[see Clinical Pharmacology (12.3)]*.

Oral Contraceptives Containing Gestodene and Ethinyl Estradiol

The co-administration of DALIRESP (500 mcg) with oral contraceptives containing gestodene and ethinyl estradiol may increase roflumilast systemic exposure and may result in increased side effects. The risk of such concurrent use should be weighed carefully against benefit *[see Clinical Pharmacology (12.3)]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic effects: Pregnancy Category C: There are no adequate and well controlled studies of DALIRESP in pregnant women. DALIRESP was not teratogenic in mice, rats, or rabbits. DALIRESP should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

DALIRESP induced stillbirth and decreased pup viability in mice at doses corresponding to approximately 16 and 49 times, respectively, the maximum recommended human dose (MRHD) (on a mg/m^2 basis at maternal doses > 2 mg/kg/day and 6 mg/kg/day, respectively). DALIRESP induced post-implantation loss in rats at doses greater than or equal to approximately 10 times the MRHD (on a mg/m^2 basis at maternal doses ≥ 0.6 mg/kg/day). No treatment-related effects on embryo-fetal development were observed in mice, rats, and rabbits at approximately 12, 3, and 26 times the MRHD, respectively (on a mg/m^2 basis at maternal doses of 1.5, 0.2, and 0.8 mg/kg/day, respectively).

Nonteratogenic effects: DALIRESP has been shown to adversely affect pup post-natal development when dams were treated with the drug during pregnancy and lactation periods in mice. These studies found that DALIRESP decreased pup rearing frequencies at approximately 49 times the MRHD (on a mg/mg^2 basis at a maternal dose of 6 mg/kg/day) during pregnancy and lactation. DALIRESP also decreased survival and forelimb grip reflex and delayed pinna detachment in mouse pups at approximately 97 times the MRHD (on a mg/m^2 basis at a maternal dose of 12 mg/kg/day) during pregnancy and lactation.

Labor and Delivery

DALIRESP should not be used during labor and delivery. There are no human studies that have investigated effects of DALIRESP on preterm labor or labor at term; however, animal studies showed that DALIRESP disrupted the labor and delivery process in mice. DALIRESP induced delivery retardation in pregnant mice at doses greater than or equal to approximately 16 times the MRHD (on a mg/m^2 basis at a maternal dose of > 2 mg/kg/day).

Nursing Mothers

Roflumilast and/or its metabolites are excreted into the milk of lactating rats. Excretion of roflumilast and/or its metabolites into human milk is probable. There are no human studies that have investigated effects of DALIRESP on breast-fed infants. DALIRESP should not be used by women who are nursing.

Pediatric Use

COPD does not normally occur in children. The safety and effectiveness of DALIRESP in pediatric patients have not been established.

Geriatric Use

Of the 4438 COPD subjects exposed to DALIRESP for up to 12 months in 8 controlled clinical trials, 2022 were > 65 years of age and 471 were > 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Based on available data for roflumilast, no adjustment of dosage in geriatric patients is warranted *[see Clinical Pharmacology (12.3)]*.

Hepatic Impairment

Roflumilast 250 mcg once daily for 14 days was studied in subjects with mild-to-moderate hepatic impairment classified as Child-Pugh A and B (8 subjects in each group). The AUCs of roflumilast and roflumilast N-oxide were increased by 51% and 24%, respectively in Child-Pugh A subjects and by 92% and 41%, respectively in Child-Pugh B subjects, as compared to age-, weight- and gender-matched healthy subjects. The C_{max} of roflumilast and roflumilast N-oxide were increased by 3% and 26%, respectively in Child-Pugh A subjects and by 26% and 40%, respectively in Child-Pugh B subjects, as compared to healthy subjects. DALIRESP 500 mcg has not been studied in hepatically impaired patients. Clinicians should consider the risk-benefit of administering DALIRESP to patients who have mild liver impairment (Child-Pugh A). DALIRESP is not recommended for use in patients with moderate or severe liver impairment (Child-Pugh B or C) *[see Contraindications (4) and Clinical Pharmacology (12.3)]*.

Renal Impairment

In twelve subjects with severe renal impairment administered a single dose of 500 mcg roflumilast, the AUCs of roflumilast and roflumilast N-oxide were decreased by 21% and 7%, respectively and C_{max} were reduced by 16% and 12%, respectively. No dosage adjustment is necessary for patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

OVERDOSAGE

Human Experience

No case of overdose has been reported in clinical studies with DALIRESP. During the Phase I studies of DALIRESP, the following symptoms were observed at an increased rate after a single oral dose of 2500 mcg and a single dose of 5000 mcg: headache, gastrointestinal disorders, dizziness, palpitations, lightheadedness, clamminess and arterial hypotension.

Management of Overdose

In case of overdose, patients should seek immediate medical help. Appropriate supportive medical care should be provided. Since roflumilast is highly protein bound, hemodialysis is not likely to be an efficient method of drug removal. It is not known whether roflumilast is dialyzable by peritoneal dialysis.

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Please also see full Prescribing Information at www.daliresp.com.

Colistin Risky but Essential for Some Critically Ill Kids

BY DIANA MAHONEY
Elsevier Global Medical News

BOSTON – Despite limited data on the safety and efficacy of colistin in children, the polymyxin antimicrobial has been used increasingly in high-risk pediatric patients as salvage therapy for serious infections caused by multidrug-resistant gram-negative bacteria, according to Dr. Pia S. Pannaraj.

"The escalating impact of antimicrobial selective pressure in high-risk pediatric populations has limited the therapeutic options available for the treatment of multidrug-resistant [MDR] gram-negative bacilli, which in turn has led to renewed interest in colistin, despite the known nephrotoxic and neurotoxic risks," she reported at the annual meeting of the Infectious Diseases Society of America.

In a study designed to review risk factors for acquiring multidrug-resistant gram-negative bacteria requiring colistin treatment and the adverse effects of such treatment in pediatric patients, Dr. Pannaraj of Childrens Hospital Los Angeles and colleagues reviewed their experience with colistin in pediatric patients admitted to their hospital between Jan. 1, 2005, and Oct. 31, 2010. Based on pharmacy records for that period, 53 children were treated with intravenous or nebulized colistin for treatment or suppressive therapy of an infection caused by MDR bacteria. Of the 53 children, 14 received 18 courses of the drug and were included in the analysis, she said. Control patients with matching underlying conditions were chosen from the medical records database.

VITALS

Major Finding: Of 14 high-risk pediatric patients, 4 experienced nephrotoxic and neurotoxic side effects from treatment with the polymyxin antimicrobial colistin, including doubled creatinine levels in 2 patients, perioral tingling in 1, and headache in 1.

Data Source: Retrospective analysis of single-institution experience with intravenous or nebulized colistin for salvage therapy of serious infections caused by multidrug-resistant gram-negative bacteria.

Disclosures: Dr. Pannaraj had no financial conflicts of interest to disclose.

MDR was defined as resistance to at least three classes of antibiotics, Dr. Pannaraj said. The underlying conditions reported in the 14 study patients included cystic fibrosis in 8, non–cystic fibrosis chronic lung disease in 3, and malignancy in 1, she said, noting that "2 of the patients were previously healthy."

Analysis showed that the children with an MDR isolate requiring colistin had more hospital days during the previous calendar year, compared with their matched controls, at 101.0 days vs. 27.2 days, respectively, Dr. Pannaraj reported. Those with MDR isolates also received more types of antibiotic than did the matched controls (6.6 vs. 4.2) for longer durations (191.0 vs. 53.8 antibiotic days).

Four gram-negative bacteria were isolated, including 16 *Pseudomonas aeruginosa*, 6 *Acinetobacter baumannii*, 3 *Klebsiella pneumoniae*, and 1 *Alcaligenes* species, with more than one pathogen isolated in seven children, she said. The indications for treatment with colistin included pulmonary exacerbation, wound infection, and bacteremia/sepsis.

Creatinine levels doubled in two children, Dr. Pannaraj reported. Two of the children developed neurologic symptoms, including perioral tingling in one and headache in another; symptoms resolved after the drug course was completed.

"We need more studies on the dosing and safety of colistin to optimize it for the treatment of high-risk children," Dr. Pannaraj said. ■

Drug May Help Kids With PAH

Sildenafil • *from page 1*

approved in the United States for this population.

The researchers measured peak oxygen consumption (V_{O_2}) and V_E/V_{CO_2} levels at the beginning of the study and again at 16 weeks in 106 children who could reliably exercise on a bicycle. The primary outcome was percent change in peak V_{O_2}. Cardiopulmonary exercise testing, rather than the more frequently used 6-minute walk test, was used to assess exercise capacity, because cardiopulmonary exercise testing is "considered a more sensitive exercise test than the 6-minute walk test; many patients have a fairly good 6-minute walk test despite significant pulmonary arterial hypertension," explained Dr. Barst, professor emeritus of pediatrics at Columbia University, New York.

'Further investigation is warranted to determine optimal dosing based on age and body weight.'

DR. BARST

Although the primary end point of percent change in peak V_{O_2} comparing the combined three sildenafil dose groups with placebo did not meet predefined criteria ($P = .056$), children in the medium- and high-dose sildenafil groups did have significantly greater improvements in peak V_{O_2} and V_E/V_{CO_2} slope, compared with those on placebo, whether the PAH was idiopathic/heritable or associated with congenital heart disease. Upper respiratory tract infections, pyrexia, and vomiting occurred more often with sildenafil than placebo. Most adverse events were mild or moderate.

Cardiopulmonary exercise testing "is a relatively simple exercise test that can be carried out safely in an exercise lab experienced in caring for children and adults with PAH," Dr. Barst said. "Measurement of ventilatory efficiency does not require the patient to exercise to maximal exertion. And there now is a more simplified gas analysis system available than what was used in this study to assess these same parameters," the Shape-HF Cardiopulmonary Testing System (Shape Medical Systems).

Limitations of the study included the fact that not all children were old enough or able to perform cardiopulmonary exercise testing. "However, all enrolled patients did have safety assessments, functional capacity evaluations, and pulmonary hemodynamic parameters obtained by invasive right heart catheterization at both baseline and at the end of the 16-week study, to obtain objective parameters of disease severity known to be prognostic for long-term outcomes," she said.

An additional limitation of most controlled studies performed in PAH, she added, is the relatively short study duration – 16 weeks in this case. "When the data from STARTS-1 [were] combined with interim data – more than 2 years – from the ongoing extension STARTS-2 study, in which all patients received active drug, the overall profile [favored] the medium dose," she said. "Further investigation is warranted to determine optimal dosing based on age and body weight."

Pfizer funded the study. Dr. Barst served as a consultant for the company during the July 2010 Food and Drug Administration advisory committee meeting on sildenafil for pediatric PAH. She has also received honoraria from Actelion, Eli Lilly, Gilead, GlaxoSmithKline, Ikaria, Merck, and Novartis. ■

Diabetes a Risk in Cystic Fibrosis

CFRD • *from page 1*

weight loss, protein catabolism, lung function decline, and increased mortality. There does not appear to be an autoimmune etiology for CFRD.

For patients with cystic fibrosis, the incidence of related diabetes is more than 50% at age 40 years. The peak age of onset for CFRD is 20-24 years, whereas type 1 diabetes is more common in children and type 2 diabetes is more common in mid-to-late adulthood, she said.

"In CFRD there is a severe insulin deficiency, but it's not as complete as in type 1," she said. CFRD is defined as the presence of at least two of the following on two occasions: fasting glucose level of at least 126 mg/dL, 2-hour oral glucose tolerance test (OGTT) of plasma glucose that is at least 200 mg/dL, or hemoglobin A_{1c} of at least 6.5% (although HbA_{1c} less than 6.5% does not exclude CFRD).

In CFRD patients, fasting glucose can range from 100 to 125 mg/dL, and a 2-hour OGTT result can range from 140 to 199 mg/dL. "So it's not quite diabetes, but it's not quite right either," she said. CFRD is "not an all or nothing kind of thing. It's not that either you have it or you don't. It can be transient in nature, and there's a spectrum," she said.

An outpatient OGTT performed when the patient is clinically stable is the test of choice for routine screening. OGTT screening is recommended annually for cystic fibrosis patients who are not already known to have diabetes, and such screening should begin by the time the patient is 10 years old.

HbA_{1c} cannot be considered a screening test for CFRD because of the high prevalence of false negatives, but a low HbA_{1c} can be used to confirm diagnosis.

Hospitalized patients who are admitted for pulmonary exacerbation and/or treatment with corticosteroids should have both fasting and 2-hour postprandial blood glucose monitoring. CFRD is diagnosed when fasting or postprandial hyperglycemia persists more than 48 hours.

Patients receiving overnight continuous drip feedings should have blood glucose monitoring midcycle to screen for CFRD. Diagnosis is based on a midcycle or immediate postfeeding glucose level of at least 200 mg/dL. This should be confirmed on two separate nights.

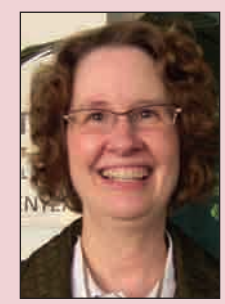
Insulin is the definitive treatment for all patients with CFRD (with or without fasting hyperglycemia). Other diabetes agents have not been shown to be of benefit in CFRD and cannot be recommended over insulin. "Insulin is the treatment of choice. Oral agents do not seem to work as well," Ms. Leonard said.

Blood glucose goals are the same as for all patients with diabetes but are adjusted for individual patient circumstances. In general, the HbA_{1c} goal is less than 7.0%.

Diet should be based on current guidelines for all cystic fibrosis patients. ■

COMMENTARY

Dr. Susan Millard, FCCP, comments: Cystic fibrosis isn't just a pediatric disease anymore. As children and adults with CF are healthier and live longer, we are learning the importance of health maintenance and watching for other CF-related problems like diabetes. CFRD was an important topic at the 25th Annual North American Cystic Fibrosis Conference in Anaheim, Calif., this November 2011.



Hia Infection Emerging in Alaskan Native Children

BY MITCHEL L. ZOLER
Elsevier Global Medical News

BOSTON – A small but concerning recent surge in cases of invasive infection with *Haemophilus influenzae* serotype a among Native Alaskan children appears to be an "emerging" infection, reported epidemiologists from the Centers for Disease Control and Prevention.

CDC epidemiologists first identified an Alaskan invasive infection by *H. influenzae* serotype a (Hia) in 2002, and by mid-October 2011 the tally stood at 27 cases in children younger than 5 years old and still rising, with 13 of the cases clustered in 2010 and 2011, Dr. Michael Bruce said at the annual meeting of the Infectious Diseases Society of America. Most of the cases have been in children younger than 5 years old and in Alaskan Native children, and most have been clustered in a specific region of western Alaska. Over the past 2 years, the Hia incidence rate among all Alaskan Native children younger than 5 years has been 15.4 cases/100,000, and among these children specifically in the western area the rate has approached about 200 cases/100,0000, "comparable to *Haemophilus influenzae* type b [Hib] in the prevaccine era," he said.

'It's alarming to us that we have this many cases. It is particularly alarming because these children are quite ill.'

DR. BRUCE

"It's alarming to us that we have this many cases" in 2010 and 2011, he said in an interview. "It is particularly alarming because these children are quite ill. Their symptoms are very similar to what we saw in the past with Hib." The most common presentation of invasive disease has been meningitis (41%), followed by pneumonia with bacteremia (26%) and septic arthritis (22%). Hospitalization was required for 89% of the 27 cases he reviewed since 2002, and two children died (a third recent death was not included in this series), he said.

"This is a serious disease, similar to Hib," said Dr. Bruce, epidemiology team leader in the Artic Investigations Program of the CDC in Anchorage. But "I don't think these [Hia cases] are temporally related to use of the Hib vaccine" which virtually eliminated Hib as a cause of invasive infections since its introduction 20 years ago.

The patients had an average age of 0.7 years (range 4 months to 2.4 years), and 63% were boys. Alaskan Native children accounted for 25 (93%) of the cases, and 93% of the patients had been appropriately vaccinated for Hib. Twenty-three (85%) of the 27 cases occurred in western Alaska.

Physicians in Alaska have generally been treating invasive Hia infections as they would invasive infections by Hib, and roughly half of the Alaskan physicians who have managed the invasive Hia cases have dispensed preventive antibiotics to close contacts, following the old Hib recommendations. So far, epidemiologic investigations in Alaska failed to identify any episodes of secondary Hia infections transmitted from an index case, Dr. Bruce said.

Recent reports of Hia clusters have come from a handful of other North American locations. "Testing for [Hia in children with invasive bacterial infections] is a good idea, especially because it is being identified in more and more places," Dr. Bruce said. "It looks to me like we did not have any cases of invasive Hia in Alaska until 2002." ■

VITALS

Major Finding: During 2002-2011, 27 Alaskan children younger than 5 years old developed an invasive infection caused by *Haemophilus influenzae* serotype a, with 13 of the cases clustering in 2010 and 2011, and 23 of the cases clustering in western Alaska. Among Alaskan Native children younger than 5 years old in western Alaska the infection rate has been about 200 cases/100,000.

Data Source: Review of cases of invasive infection with *H. influenzae* serotype a in Alaskan children younger than 5 years old during 2002-2011.

Disclosures: Dr. Bruce said that he had no disclosures.

New Formulation of Flu Vax Found Effective in Children

BY MARY ANN MOON
Elsevier Global Medical News

An adjuvant trivalent inactivated influenza vaccine in an oil-and-water emulsion that augments the immune response was found to be effective in a field trial of 4,707 German and Finnish children.

The novel vaccine showed 86% efficacy against all circulating viral strains of influenza during the 2 years of the trial, and 89% efficacy against vaccine-matched strains. In contrast, efficacy rates for the standard trivalent inactivated flu vaccine, which is known to be poorly immunogenic in children, were 43% and 45%, respectively, said Dr. Timo Vesikari of the University of Tampere (Finland) and his associates.

The oil-in-water emulsion (MF59), which enhances the immune response when combined with vaccine antigens, has been used since 1997 in the influenza vaccine for older adults, and has been licensed in 27 countries. In an earlier study, Dr. Vesikari and his colleagues reported that it induced a greater immune response in children aged 6-36 months than did the standard vaccine formulation.

They now report the results of a phase III trial in 654 children in Germany in year 1, as well as 2,104 children in Germany and 1,949 in Finland during year 2. These study subjects were 6-71 months old.

The study participants were randomly assigned to one of three groups: the novel vaccine group (1,941 patients), those receiving the standard subunit trivalent inactivated vaccine that is poorly immunogenic in children (1,773 patients), or a control group receiving non-influenza vaccine (993 patients).

The vaccines were administered in two doses, 1 month apart.

The absolute efficacy of the novel vaccine for both influenza seasons was 86% against all strains and 89% against vaccine-matched strains and the influenza A(H3N2) virus. In contrast, the standard vaccine had an efficacy of 43% against all strains and 45% against vaccine-matched strains and the H3N2 virus.

When the data were broken down by patient age, the novel vaccine showed efficacy against 64% of all strains and 68% of matched strains among children aged 6-35 months, and against 86% of all strains and 91% of matched strains among children aged 36-71 months, the investigators said (N. Engl. J. Med. 2011;365:1406-16).

Moreover, the study subjects frequently showed an immune response after the first dose of the novel vaccine, unlike with the standard or control vaccines.

At ages 6-35 months, rates of seroprotection against influenza A (H1N1) and H3N2 strains after one dose were 92% and 95%, respectively, with the novel vaccine. The corresponding rates of seroprotection after one dose of the standard vaccine were 20% and 12%, respectively.

In children aged 36-71 months of age, these proportions after one dose were 100% and 97% for the novel vaccine, compared with 63% and 60% for the standard vaccine.

Vaccine-related adverse events were generally mild to moderate and were similar across the three vaccine groups in the younger patients. In older patients aged 36-71 months, "systemic reactions, including mild fever, were slightly more frequent after receipt of the [novel] vaccine, as compared with the other vaccines, but these reactions were mostly mild and of short duration," Dr. Vesikari and his associates said. ■

VITALS

Major Finding: A novel formulation of the flu vaccine that augments the immune response showed 86% efficacy against all strains and 89% efficacy against vaccine-matched strains in a pediatric population.

Data Source: A phase III field trial comparing the efficacy of a special formulation of the flu vaccine and the standard formulation during two flu seasons in 4,707 children in Germany and Finland.

Disclosures: This study was funded by Novartis Vaccines. Novartis employees also designed and conducted the study and analyzed the data. Dr. Vesikari and his associates reported ties to Astra Zeneca, GlaxoSmithKline, MedImmune, Merck, Pfizer, Sanofi Pasteur, SPMSD, and Wyeth.

Fostering Meaningful Communication at Life's End

BY DOUG BRUNK
Elsevier Global Medical News

HONOLULU – What do patients in the ICU want at the end of life?

Research has shown that pain control typically ranks at the top of the list, "but they also want to avoid inappropriate prolongation of dying," Dr. Richard Mularski, FCCP, said at the annual meeting of the American College of Chest Physicians.

Patients "want to achieve a sense of control at the end of life," continued Dr. Mularski, a pulmonologist who is a clinical investigator with the Center for Health Research at Kaiser Permanente Northwest, Portland, Ore. "They don't want to be a burden on their family. We have to offer professional help, which primarily comes from talking with our patients and providing opportunities to strengthen relationships with loved ones. This might mean backing off on sedatives and pain medications so that patients and loved ones can interact before withdrawal of life support."

Dr. Mularski highlighted four key points from a 2009 consensus statement he helped to create on pain management during the palliative and end-of-life experience in the ICU (Chest 2009; 135:1360-9). The first point reads that all ICU patients "experience opportunities for discomfort and suffering regardless of prognosis or goals, thus palliative therapy is a requisite approach for every patient, of which pain management is a principal component."

According to the second, third, and fourth key points, "for those dying in the ICU, an explicit shift in management to comfort-oriented care is often warranted and may be the most beneficial treatment the health-care team can offer; communication and cultural sensitivity with the patient-family unit is a principal approach for optimizing palliative and pain management as part of comprehensive ICU care, [and] ethical and legal misconceptions about the escalation of opiates and other palliative therapies should not be barriers to appropriate care, provided the intention of treatment is alleviation of pain and suffering."

Communicating effectively with the patient and family about prognosis in the critical care setting can be difficult "because we're often limited by what treatments or interventions we can make," Dr. Mularski said. "This creates a certain tension: Patients have a widespread and deeply held desire not to be dead. We have to try to focus on that desire and acknowledge our limitations. Data show we don't really prognosticate when death will occur very well."

The limited options for treatment are only part of the problem. A trial conducted in a university-affiliated ICU found that 54% of families fail to comprehend a diagnosis, a prognosis, or treatment options (Crit. Care Med. 2000;28:3044-9). "We also know that family members experience a fair amount of moderate to severe posttraumatic stress," Dr. Mularski added. "This stress is increased when we provide inadequate information. We have to be careful not to use phrases that

COMMENTARY

Dr. Paul Selecky, FCCP, comments: I wholeheartedly agree with Dr. Mularski's overview and the observed need for communication between the care team and patient/family in the ICU setting. The obstacles are many, which urges us to begin this communication long before a critical illness occurs. We need to present an opportunity for advance care planning to all our patients who have an ongoing chronic disease such as COPD, CHF, advanced lung cancer, or IPF. It is the so-called "ventilator talk" we all try to have with our patients to determine their wishes regarding the intensity of treatment, and at the same time asssuring them that we will do everything we can to minimize their suffering, principally severe dyspnea as the disease progresses.

suggest abandonment or a failure of medicine to care, such as 'there's nothing more we can do,' or 'we have nothing to offer.' We have plenty to offer. Palliative care may be the most important thing we have to offer at the end of life."

Key factors in shared decision making between clinicians and families about end-of-life care include prognosis, level of certainty "which may not be there," and family preferences. "The role of the patient and family is to help us understand patient values and preferences, and for us as clinicians to indicate which treatments might be concurrent with those values and preferences," Dr. Mularski said.

In a 2008 article, "Practical Guidance for Evidence-Based ICU Family Conferences," Dr. J. Randall Curtis and Dr. Douglas B. White offered a five-step approach to improving communication in the ICU with families (Chest 2008;134:835-43). It centers on the mnemonic "VALUE," which stands for value family statements, acknowledge family emotions, listen to the family, understand the patient as a person, and elicit family questions.

'Palliative care may be the most important thing we have to offer at the end of life.'

DR. MULARSKI

At Kaiser Permanente Northwest, Dr. Mularski and his colleagues created pocket cards for critical care staff that contain the VALUE mnemonic to remind them of how to best interact with families of patients in the ICU. He also recommends the book by Dr. Anthony L. Back and colleagues, "Mastering Communication with Seriously Ill Patients: Balancing Honesty with Empathy and Hope" (New York: Cambridge University Press, 2009).

Dr. Mularski disclosed that he has received research funding from several agencies including the Agency for Healthcare Research and Quality, National Cancer Institute, National Quality Forum, and Robert Wood Johnson Foundation. He also has received research support from Novartis and Spiration for unrelated work in COPD. ■

Sleep Apnea Worsens Psychiatric Symptoms

VITALS

Major Finding: Of 85 psychiatric patients screened with the STOP-Bang questionnaire, 14 were ultimately diagnosed with obstructive sleep apnea.

Data Source: Screening study of adult community hospital psychiatric inpatients.

Disclosures: Dr. Jain said she has no disclosures.

BY M. ALEXANDER OTTO
Elsevier Global Medical News

SAN FRANCISCO – A simple questionnaire can pick up obstructive sleep apnea in psychiatric patients, according to a small study.

Screening is rare in psychiatric patients at present, but it's important to diagnose obstructive sleep apnea (OSA) because it can make mental illness worse, contributing to depression and possibly to the risk of manic episodes. Symptoms can mimic mental illness as well, making patients irritable and tired, and OSA makes the use of benzodiazepines and other respiratory depressants problematic, said lead investigator Dr. Vanita Jain, a psychiatry department resident at the University of Utah, Salt Lake City. "Sleep problems are so integral to psychiatric problems, [and] we wanted to make sure that along with psychiatric disorders, we were treating obstructive sleep apnea, too," she said.

The researchers screened 85 adult community hospital psychiatric inpatients with the STOP-Bang questionnaire, which is typically used as a presurgery screen and takes less than 2 minutes to fill out.

The name refers to the survey's eight yes/no questions: Do you snore loudly? Do you often feel tired, fatigued, or sleepy during daytime? Has anyone observed you stop breathing during your sleep? Do you have or are you being treated for high blood pressure? Body mass index

more than 35 kg/m^2? Age over 50 years? Neck circumference greater than 40 cm? Gender male?

Most of the 85 subjects were white, and more than half were men. In all, 46 of the subjects answered yes to at least three of the eight questions, which is considered a positive screen.

Those patients had overnight pulse oximetry monitoring; 26 desaturated more than 10 times per hour. Fifteen of the 26 – most of the rest had been discharged or refused additional testing – underwent a polysomnography sleep study. Fourteen were ultimately diagnosed with OSA; three had more than 30 apneic episodes per hour.

They would have gone undiagnosed were it not for the questionnaire, Dr. Jain said at the American Psychiatric Association's Institute on Psychiatric Services.

Psychiatric patients can complicate OSA work-up. In the current study, for example, when patients were not coherent enough for an overnight stay in the sleep lab or if they were an escape risk, polysomnography was conducted in their rooms. If patients were "very psychotic or agitated," they were asked to return for an outpatient sleep study, Dr. Jain said. ■

COMMENTARY

Dr. Paul Selecky, FCCP, comments: This study supports the value of screening certain patient groups for a possible sleep-related breathing disorder, as previously demonstrated in patients with CHF or COPD. Screening of all inpatients clinically by the admitting nurse is done in some hospitals, focusing on the patient's sleep history with the STOP-Bang or other screening tool. Some hospitals then use sleep oximetry or other screening device for those at high risk as established by the questionnaire. Others would argue that these results may be misleading because of the possible instability in an acute illness. If you are considering doing this at your institution, the best results are generally achieved by a coordinated multidisciplinary team of nurses, respiratory therapists, sleep technologists, and physicians.

If clinically significant fluid retention develops, with or without associated weight gain, further evaluation should be undertaken to determine the cause, such as Tracleer or underlying heart failure, and the possible need for treatment or discontinuation of Tracleer therapy.

Decreased Sperm Counts

An open-label, single arm, multicenter, safety study evaluated the effect on testicular function of Tracleer 62.5 mg twice daily for 4 weeks, followed by 125 mg twice daily for 5 months. Twenty-five male patients with WHO functional class III and IV PAH and normal baseline sperm count were enrolled. Twenty-three completed the study and 2 discontinued due to adverse events not related to testicular function. There was a decline in sperm count of at least 50% in 25% of the patients after 3 or 6 months of treatment with Tracleer. Sperm count remained within the normal range in all 22 patients with data after 6 months and no changes in sperm morphology, sperm motility, or hormone levels were observed. One patient developed marked oligospermia at 3 months and the sperm count remained low with 2 follow-up measurements over the subsequent 6 weeks. Tracleer was discontinued and after two months the sperm count had returned to baseline levels. Based on these findings and preclinical data from endothelin receptor antagonists, it cannot be excluded that endothelin receptor antagonists such as Tracleer have an adverse effect on spermatogenesis.

Decreases in Hemoglobin and Hematocrit

Treatment with Tracleer can cause a dose-related decrease in hemoglobin and hematocrit. It is recommended that hemoglobin concentrations be checked after 1 and 3 months, and every 3 months thereafter. If a marked decrease in hemoglobin concentration occurs, further evaluation should be undertaken to determine the cause and need for specific treatment.

The overall mean decrease in hemoglobin concentration for bosentan-treated patients was 0.9 g/dL (change to end of treatment). Most of this decrease of hemoglobin concentration was detected during the first few weeks of bosentan treatment and hemoglobin levels stabilized by 4–12 weeks of bosentan treatment. In placebo-controlled studies of all uses of bosentan, marked decreases in hemoglobin (> 15% decrease from baseline resulting in values < 11 g/dL) were observed in 6% of bosentan-treated patients and 3% of placebo-treated patients. In patients with PAH treated with doses of 125 and 250 mg twice daily, marked decreases in hemoglobin occurred in 3% compared to 1% in placebo-treated patients.

A decrease in hemoglobin concentration by at least 1 g/dL was observed in 57% of bosentan-treated patients as compared to 29% of placebo-treated patients. In 80% of those patients whose hemoglobin decreased by at least 1 g/dL, the decrease occurred during the first 6 weeks of bosentan treatment. During the course of treatment the hemoglobin concentration remained within normal limits in 68% of bosentan-treated patients compared to 76% of placebo patients. The explanation for the change in hemoglobin is not known, but it does not appear to be hemorrhage or hemolysis.

Pulmonary Veno-Occlusive Disease

Should signs of pulmonary edema occur when Tracleer is administered, the possibility of associated pulmonary veno-occlusive disease should be considered and Tracleer should be discontinued.

Prescribing and Distribution Program for Tracleer

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

To enroll in T.A.P., prescribers must complete the T.A.P. Tracleer (bosentan) Enrollment and Renewal Form (see T.A.P. Tracleer (bosentan) Enrollment and Renewal Form for full prescribing physician agreement) indicating agreement to:

- Read and understand the communication and educational materials for prescribers regarding the risks of Tracleer.
- Review and discuss the Tracleer Medication Guide and the risks of bosentan (including the risks of teratogenicity and hepatotoxicity) with every patient prior to prescribing Tracleer.
- Review pretreatment liver function tests (ALT/AST/bilirubin) and, for females of childbearing potential, confirm that the patient is not pregnant.
- Agree to order and monitor monthly liver function tests and, for females of childbearing potential, pregnancy tests.
- Enroll all patients in T.A.P. and renew patients' enrollment annually thereafter.
- Educate and counsel females of childbearing potential to use reliable contraception, as defined on the Tracleer Enrollment and Renewal Form, during treatment with Tracleer and for one month after treatment discontinuation.
- Counsel patients who fail to comply with the program requirements.
- Notify Actelion Pharmaceuticals US, Inc. of any adverse events, including liver injury, and report any pregnancy during Tracleer treatment.

Throughout treatment and for one month after stopping Tracleer, females of childbearing potential must use two reliable methods of contraception unless the patient has a tubal sterilization or Copper T 380A IUD or LNg 20 IUS inserted, in which case no other contraception is needed. Hormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives should not be used as the sole means of contraception because these may not be effective in patients receiving Tracleer.

ADVERSE REACTIONS

The following important adverse reactions are described elsewhere in the labeling:

Potential liver injury [see **Boxed Warning, Warnings and Precautions**]

Fluid retention [see **Warnings and Precautions**]

Clinical Studies Experience

Safety data on bosentan were obtained from 13 clinical studies (9 placebo-controlled and 4 open-label) in 870 patients with pulmonary arterial hypertension and other diseases. Doses up to 8 times the currently recommended clinical dose (125 mg twice daily) were administered for a variety of durations. The exposure to bosentan in these trials ranged from 1 day to 4.1 years (N=94 for 1 year; N=61 for 1.5 years and N=39 for more than 2 years). Exposure of pulmonary arterial hypertension patients (N=328) to bosentan ranged from 1 day to 1.7 years (N=174 more than 6 months and N=28 more than 12 months).

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

Treatment discontinuations due to adverse events other than those related to pulmonary hypertension during the clinical trials in patients with pulmonary arterial hypertension were more frequent on bosentan (6%; 15/258 patients) than on placebo (3%; 5/172 patients). In this database the only cause of discontinuations > 1% and occurring more often on bosentan was abnormal liver function.

The adverse drug events that occurred in ≥3% of the bosentan-treated patients and were more common on bosentan in placebo-controlled trials in pulmonary arterial hypertension at doses of 125 or 250 mg twice daily are shown in Table 2:

Adverse events* occurring in ≥3% of patients treated with bosentan 125-250 mg twice daily and more common on bosentan in placebo-controlled studies in pulmonary arterial hypertension

Adverse Event	Bosentan N=258		Placebo N=172	
	No.	%	No.	%
Respiratory Tract Infection	56	22%	30	17%
Headache	39	15%	25	14%
Edema	28	11%	16	9%
Chest Pain	13	5%	8	5%
Syncope	12	5%	7	4%
Flushing	10	4%	5	3%
Hypotension	10	4%	3	2%
Sinusitis	9	4%	4	2%
Arthralgia	9	4%	3	2%
Liver Function Test Abnormal	9	4%	3	2%
Palpitations	9	4%	3	2%
Anemia	8	3%	–	

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

Combined data from Study-351, BREATHE-1 and EARLY

Postmarketing Experience

There have been several post-marketing reports of angioedema associated with the use of bosentan. The onset of the reported cases occurred within a range of 8 hours to 21 days after starting therapy. Some patients were treated with an antihistamine and their signs of angioedema resolved without discontinuing Tracleer.

The following additional adverse reactions have been reported during the post approval use of Tracleer. Because these adverse reactions are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Tracleer exposure:

- Unexplained hepatic cirrhosis [see **Boxed Warning**]
- Liver failure [see **Boxed Warning**]
- Hypersensitivity [see **Contraindications**]
- Thrombocytopenia
- Rash
- Jaundice
- Anemia requiring transfusion
- Neutropenia and leukopenia

DRUG INTERACTIONS

Cytochrome P450 Summary

Bosentan is metabolized by CYP2C9 and CYP3A. Inhibition of these enzymes may increase the plasma concentration of bosentan (see ketoconazole). Concomitant administration of both a CYP2C9 inhibitor (such as fluconazole or amiodarone) and a strong CYP3A inhibitor (e.g., ketoconazole, itraconazole) or a moderate CYP3A inhibitor (e.g., amprenavir, erythromycin, fluconazole, diltiazem) with bosentan will likely lead to large increases in plasma concentrations of bosentan. Co-administration of such combinations of a CYP2C9 inhibitor plus a strong or moderate CYP3A inhibitor with Tracleer is not recommended.

Bosentan is an inducer of CYP3A and CYP2C9. Consequently plasma concentrations of drugs metabolized by these two isozymes will be decreased when Tracleer is co-administered. Bosentan had no relevant inhibitory effect on any CYP isozyme in vitro (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A). Consequently, Tracleer is not expected to increase the plasma concentrations of drugs metabolized by these enzymes.

Hormonal Contraceptives

Hormonal contraceptives, including oral, injectable, transdermal, and implantable forms, may not be reliable when Tracleer is co-administered. Females should practice additional methods of contraception and not rely on hormonal contraception alone when taking Tracleer [see **Boxed Warning, Contraindications**].

An interaction study demonstrated that co-administration of bosentan and a combination oral hormonal contraceptive produced average decreases of norethindrone and ethinyl estradiol levels of 14% and 31%, respectively. However, decreases in exposure were as much as 56% and 66%, respectively, in individual subjects.

Cyclosporine A

The concomitant administration of bosentan and cyclosporine A is contraindicated [see **Contraindications**].

During the first day of concomitant administration, trough concentrations of bosentan were increased by about 30-fold. The mechanism of this interaction is most likely inhibition of transport protein-mediated uptake of bosentan into hepatocytes by cyclosporine. Steady-state bosentan plasma concentrations were 3- to 4-fold higher than in the absence of cyclosporine A. Co-administration of bosentan decreased the plasma concentrations of cyclosporine A (a CYP3A substrate) by approximately 50%.

Glyburide

An increased risk of elevated liver aminotransferases was observed in patients receiving concomitant therapy with glyburide. Therefore, the concomitant administration of Tracleer and glyburide is contraindicated, and alternative hypoglycemic agents should be considered [see **Contraindications**].

Co-administration of bosentan decreased the plasma concentrations of glyburide by approximately 40%. The plasma concentrations of bosentan were also decreased by approximately 30%. Bosentan is also expected to reduce plasma concentrations of other oral hypoglycemic agents that are predominantly metabolized by CYP2C9 or CYP3A. The possibility of worsened glucose control in patients using these agents should be considered.

KPC Infections May Not Be as Deadly as Thought

BY SUSAN LONDON
Elsevier Global Medical News

CHICAGO – The prognosis for patients with infections caused by Enterobacteriaceae that harbor *Klebsiella pneumoniae* carbapenemase (KPC) may not be as poor as some statistics have suggested, according to a small study of patients with bloodstream infections due to these resistant pathogens.

The 30-day mortality rate in the study of 39 patients was 13% – or roughly half to a third of that seen in previous studies – researchers reported at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy. Moreover, 41% of the patients did not even receive an antibiotic active against KPC-positive pathogens.

"There has been a really high mortality associated with this type of infection," lead investigator Elizabeth B. Hirsch, Pharm.D., of Northeastern University in Boston, commented in an interview. "Some people are reporting from 30% to 50% mortality with this type of infection, so we were a little bit surprised at that [13% rate]."

The study also found that a greater severity of illness, as assessed by Acute Physiology and Chronic Health Evaluation (APACHE) II scores, independently predicted death in this population, which may in part explain the disparate findings, she speculated. "Maybe in other studies reporting such high mortality rates, it's just that patients at baseline are very sick, and it's not necessarily attributed to having the KPC."

The investigators studied 39 patients with bloodstream infections due to KPC-harboring Enterobacteriaceae treated between May 2009 and December 2010. Study results were reported in a poster session at the meeting, which was sponsored by the American Society for Microbiology.

VITALS

Major Finding: The 30-day rate of mortality in infected patients was 13%. Greater severity of illness and younger age were independently associated with poorer prognosis.

Data Source: An observational cohort study of 39 patients with bloodstream infections caused by KPC-harboring Enterobacteriaceae.

Disclosures: Dr. Hirsch reported having no conflicts of interest related to the study.

The patients were 62 years old, on average; 54% were male and 36% were white. They had been hospitalized for a mean of 27 days, and their mean APACHE II score was 12.4.

The most common source of the bacteremia was abdominal (39%), followed by urinary (26%) and pulmonary (15%). In terms of the specific pathogen, 61.5% of patients had *Klebsiella* species, 36% had *Escherichia coli*, and 2.5% had *Enterobacter aerogenes*.

Overall, 13% of the patients died in the 30 days after diagnosis. In a multivariate analysis, patients with an APACHE II score of 17 or higher were more likely to die (odds ratio, 45.4; $P = .013$), whereas the risk of death fell with advancing age (OR, 0.9; $P = .038$).

"Surprisingly, a lot of these patients didn't even receive any therapy that was active against the KPC, but they cleared their bloodstream infection [anyway]," noted Dr. Hirsch.

Specifically, 16 patients did not receive any KPC-active therapy. In this subset, the most common source of bacteremia was urinary (44%) and the 30-day mortality rate was the same as that in the cohort overall (13%).

Given the high prevalence of a urinary source of infection in this group, "if they are receiving carbapenems, which we know the KPC can hydrolyze, maybe they are getting high enough concentrations of the drug in the urine, which I guess is sort of clearing the main source of infection," she said.

Molecular analyses in the overall cohort identified 14 unique clones among the *Klebsiella* isolates and 7 unique clones among the *E. coli* isolates.

"Since we found a lower rate of mortality [than previously reported], we are kind of wondering what the virulence is associated with these isolates," Dr. Hirsch concluded. "So that's the next step – we are going to do some analyses of the isolates to see really how virulent they are." ■

SAVE Helps Manage Septic Shock

BY SHERRY BOSCHERT
Elsevier Global Medical News

SAN FRANCISCO – To save a patient in septic shock, think SAVE.

The acronym stands for Suspicion, Act, Ventilation/oxygenation, and Evaluate the goals, Dr. Robert J. Vissers said at the annual meeting of the American College of Emergency Physicians. He adapted the SAVE acronym from the 2011 Critical Points continuing medical education course for emergency physicians.

Suspicion starts with recognizing systemic inflammatory response syndrome (SIRS), which combined with an infection constitutes sepsis. Patients have SIRS if they have at least two of the following: temperature higher than 38° C or below 36° C; heart rate faster than 90 beats per minute; white blood cell count over 12,000 or less than 4,000 cells/mcL or with greater than 10% bands (immature forms); and a respiratory rate over 20 breaths per minute or, on blood gas, a partial pressure of carbon dioxide less than 32 mm Hg.

Patients with sepsis and organ dysfunction, hypoperfusion, or hypotension have severe sepsis; they have septic shock if the hypotension or hypoperfusion is refractory to fluid resuscitation, said Dr. Vissers, chief of emergency medicine at Legacy Emanuel Hospital, Portland, Ore.

The shock index (the ratio of heart rate divided by systolic blood pressure) is a simple calculation that can help fuel or allay suspicion of septic shock, he said. A normal ratio is 0.5-0.7, while 1.0 or greater may predict uncompensated shock.

The second step in SAVE is to act by perfusing the patient and giving the right antibiotics.

Fill the patient's "tank" by aggressively giving fluids in serial 500- to 1,000-mL boluses of normal saline, he said. Often, 50-60 mL/kg are needed. "The fluids are about a liter every 30 minutes, if you think you've got someone with severe sepsis or septic shock. Four to six liters is not unusual before you fill the tank."

Early goals in perfusion should be a mean arterial pressure greater than 65 mm Hg, urine output greater than 0.5 mL/kg per hour, and signs of clinical improvement such as waking up.

Tighten the patient's perfusion "hose" by administering pressors when the "tank" is full and central venous pressure measures 8-12 mm Hg or ultrasound assessment of the inferior vena cava (IVC) shows greater than a 50% collapse of the IVC on breathing, which is suggestive of a central venous pressure less than 8 mm Hg.

Use norepinephrine or dopamine; there's no evidence that one pressor is better than another, he said. Delay in antibiotics is associated with significantly higher mortality, so aim to give antibiotics within an hour of triage or diagnosis. Giving inappropriate antibiotics increases the risk of death two- to fivefold. If the infection has an unknown source, treat with vancomycin plus piperacillin-tazobactam, ticarcillin-clavulanate, ceftriaxone, cefotaxime, imipenem, or meropenem.

Early initiation of mechanical ventilation/oxygenation is the third part of SAVE. Septic shock makes breathing harder, which can lead to hypoxia and acidosis and produces a 50% chance of adult respiratory distress syndrome. To reduce potential lung damage, Dr. Vissers recommended these ventilator settings: a low tidal volume of 6 cc/kg of ideal body weight and plateau pressure less than 30 cm H_2O.

Last, evaluate the goals to SAVE a patient in septic shock. If lactate does not decrease by 10% or central venous oxygen saturation is less than 70% and the hemoglobin level is less than 7 g/dL, transfuse packed red blood cells. If the mean arterial pressure is less than 65 mm Hg despite optimal fluids and a pressor, consider giving IV hydrocortisone 100 mg and packed red blood cells if the hemoglobin is less than 10 g/dL. If the mean arterial pressure is greater than 65 mm Hg but the patient is still underperfused, consider giving inotropic dobutamine.

Dr. Vissers said he has no relevant conflicts of interest. ■

COMMENTARY

Dr. Steven Simpson, FCCP, comments: Dr. Vissers presents to emergency medicine physicians some principles with which ACCP members are likely to be familiar and that are concordant with the Surviving Sepsis Guidelines. Since more than half of severe sepsis and septic shock patients present to the emergency department, it is of utmost importance that resuscitation of these patients begins immediately in the ED. When intensivists and ED physicians work in concert, patients' risk of dying can be substantially reduced, ICU and hospital days can be shortened, and posthospital recovery can be faster and more complete.

FROM THE DESK OF THE PRACTICE MANAGEMENT COMMITTEE

PMC Year in Review and New ICD-9-CM, CPT Codes for 2012

BY DR. ROBERT DEMARCO, FCCP, CHAIR; DONNA KNAPP, MA, FACMPE, VICE-CHAIR; AND DIANE KRIER-MORROW, MBA, MPH, CCS-P, ACCP CODING AND REIMBURSEMENT CONSULTANT

Dr. Robert DeMarco, Chair of the Practice Management Committee (PMC), and Donna Knapp, Vice-Chair, are using this opportunity to summarize the work of the PMC this past year. The ACCP is very appreciative of the work put in by all of its members of the PMC and the ACCP staff throughout the year. In particular, we thank Dr. Steve Peters, FCCP, the ACCP CPT Advisor; Dr. Mike Nelson, FCCP, the ACCP Alternate CPT Advisor; Dr. Kathrin Nicolacakis, FCCP, the ACCP RUC Advisor; Dr. Scott Manaker, PhD, FCCP, the RUC member for internal medicine; and Dr. Burt Lesnick, FCCP, the alternate RUC member.

In January, the PMC decided that monthly communication through *CHEST Physician* and the weekly *NewsBrief* are essential for keeping the membership and their staff current on PMC activities. An example of how the *NewsBrief* has been utilized is by sending reminders of the looming deadline for June 30 to electronically prescribe 10 unique patient prescriptions in order to avoid the penalty for all Medicare allowed charges for 2012.

Numerous articles discussed several important topics in *CHEST Physician* this year and should be shared with practice staff (see table).

During the summer, the PMC conducted a marketing survey to determine if a print or an electronic edition is the preference for the ACCP book, *Coding for Chest Medicine*. The PMC thanks the members who completed the survey. The PMC decided not to print a book for 2012 and to provide the membership with coding changes through articles in *CHEST Physician*. The September article was dedicated to ICD-9-CM codes effective October 1, 2011, especially the new adult/children interstitial lung disease (ILD) codes. The November issue published two articles, one on new and deleted pulmonary function testing (PFT) codes and the other on bronchoscopy with the new tracking codes for bronchial thermoplasty.

For 2012, there are major diagnostic code changes with 54 new ICD-9-CM codes that may be of interest to providers in the practice, 10 deleted PFT codes replaced by 4 new codes and significantly expanded introductory language, new Bronchial Thermoplasty Category III tracking codes and new introductory language and definitions for the sleep family of codes in the AMA CPT® book.

ICD-9-CM Diagnosis Codes

There are several new diagnosis codes that drive and support medical necessity for the services and procedures you perform. In the September *CHEST Physician*, PMC provided a table of the **516.3-516.8** ILD codes, including the new 5th-digit codes for children, **516.61-516.69**. The **793.11-793.19** pulmonary nodule codes were noted. (Other new codes are listed in the table at right, bottom.)

It is important to check that your entire practice is reporting new 4th and 5th digit diagnosis codes as of October 1, 2011, or your reimbursements will be denied. Again, official ICD-9-CM annual code revisions are referred to as addenda and the first volume of the addenda index is available on the National Center for Health Statistics (NCHS) Web site at www.cdc.gov/nchs/data/icd9/ICD-9-CMINDEXADDENDAfy12.pdf. The tabular list of diseases addenda (Volume II) can be viewed at www.cdc.gov/nchs/data/icd9/ICD-9-CM%20TABULARADDENDAfy12.pdf. When you review the source addenda, check both the Diagnoses Index and the Tabular List for selection of the appropriate codes to report.

PFTs

CPT added a new header: "Pulmonary Diagnostic Testing and Therapies" to the PFT section of CPT. The 10 CPT PFT codes deleted are: **93720-93722, 94240, 94260, 94350, 94360, 94370, 94720 and 94725**. The rationale for this change, by a directive from Medicare to bundle the PFT codes through the AMA RUC process, was that certain codes had duplicative reimbursement for pre-service and post-service times included in the payment. If your practice reports any of these deleted codes on a claim in 2012, the claim will not be processed, which will negatively affect cash flow in your practice.

New PFT Lung Volumes will be reported by the equipment used – **94726** plethysmography, **94727** gas dilution/washout or **94728** oscillometry. **+94729** is an add-on code for diffusing capacity. CPT **94726**, **94727**, and **+94729** may be reported with spirometry (**94010**, **94060** or **94375**).

PFT Introductory Notes in CPT 2012

Codes **94010-94799** include laboratory procedure(s) and interpretation of pulmonary function test results. If a separate identifiable Evaluation and Management service is performed, the appropriate E/M service code may be reported in addition to **94010-94799**.

Spirometry (**94010**) measures expiratory airflow and volumes and forms the basis of most pulmonary function testing. When spirometry is performed before and after administration of a bronchodilator, report **94060**. Measurement of vital capacity (**94150**) is a component of spirometry and is only reported when performed alone. The flow-volume loop (**94375**) is used to identify patterns of inspiratory and/or expiratory obstruction in central or peripheral airways.

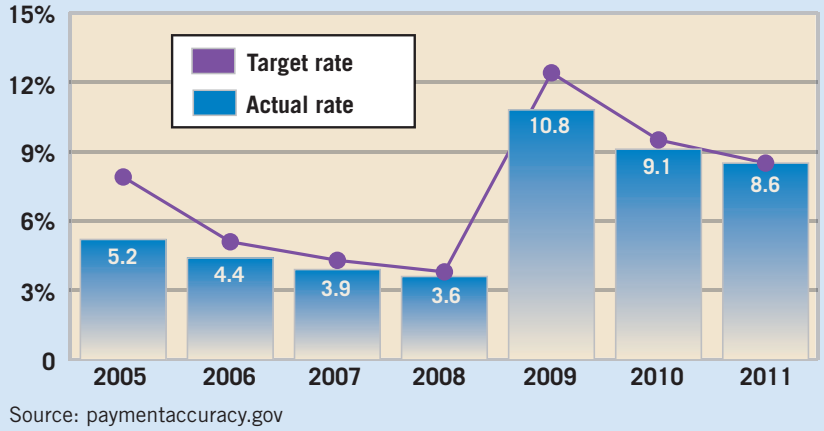
Spirometry (**94010**, **94060**) includes maximal breathing capacity (MBC), or maximal voluntary ventilation (MVV) (**94200**) and flow-volume loop (**94375**), when performed.

Measurement of lung volumes may be performed using plethysmography or gas dilution. Plethysmography (**94726**) is utilized to determine total lung capacity, residual volume, functional residual capacity, and airway resistance. Nitrogen washout or helium dilution (**94727**) may be used to measure lung volumes, distribution of ventilation and closing volume. Impulse oscillometry (**94728**) assesses airway resistance and may be reported in addition to gas dilution techniques. Spirometry is not reported in addition to oscillometry. Spirometry (**94010**,

CHEST Physician 2011 Issue	Topic
February	2011 Medicare Physician Fee Schedule (includes table comparing 2010 and 2011 Sleep codes)
March	ICD-10-CM
April	Physician Quality Research System (PQRS) Information and Current Procedure Terminology (CPT) Process
May	AMA/Specialty Society Relative Update (RUC) Process and Electronic Health Records (EHR) Incentive Program
June	Accountable Care Organizations
July	PMC EHR Subcommittee and HIMSS
August	Medicare Administrative Contractor Advisory Committee and Top Practice Management Tips
September	Interstitial Lung Disease ICD-9-CM
October	Preparing for Retirement
November	PFTs and Bronchoscopy - New for 2012

New ICD-9-CM Code Number	ICD-9-CM Diagnosis Descriptor
348.82	Brain Death
512.81	Primary spontaneous pneumothorax
518.51	Acute respiratory failure following trauma and surgery
795.51	Nonspecific reaction to tuberculin skin test without active tuberculosis
997.32	Postprocedural aspiration pneumonia
998.02	Postoperative shock, septic
V12.55	Personal history of Pulmonary embolism

Historical Improper Payment Rates for Medicare Fee-for-Service



Source: paymentaccuracy.gov

New CPT Codes for 2012

94726 Plethysmography for determination of lung volumes and, when performed, airway resistance

94727 Gas dilution or washout for determination of lung volumes and, when performed, distribution of ventilation and closing volumes

94728 Airway resistance by impulse oscillometry

+94729 Diffusing capacity (e.g., carbon monoxide, membrane)

Bronchial Thermoplasty Category III codes:

0276T Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with bronchial thermoplasty, 1 lobe

0277T Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with bronchial thermoplasty, 2 or more lobes

Note

Deleted 10 PFT codes: 93720-93722, 94240, 94260, 94350, 94360, 94370, 94720, 94725

Introductory Language for Sleep codes **95800-95811**

Significant ICD-9-CM Code Changes: 4th and 5th digits for Interstitial Lung Disease diagnosis codes, new single/multiple pulmonary nodule codes, air leaks

94060) and bronchial provocation (**94070**) are not included in **94726** and **94727** and may be reported separately.

Diffusing capacity (**+94729**) is most commonly performed in conjunction with lung volumes or spirometry and is an add-on code to **94726-94728**, **94010**, **94060**, **94070**, and **94375**.

Pulmonary function tests (**94011-94013**) are reported for measurements in infants and young children through 2 years of age.

Pulmonary function testing measurements are reported as actual values and as a percent of predicted values by age, gender, height, and race.

2012 New Sleep Introductory Language

Sleep medicine services include procedures that evaluate adult and pediatric patients for a variety of sleep disorders. Sleep medicine testing services are diagnostic procedures using in-laboratory and portable technology to assess physiologic data and therapy.

All sleep services (**95800-95811**) include recording, interpretation and the written report. (Report with modifier **52** if less than 6 hours of recording for **95800**, **95801**-unattended sleep, and **95806-95811**, and if less than four nap opportunities are recorded for 95805).

*Definitions are provided for "Actigraphy," "Attended," "Electrooculogram (EOG)," "Maintenance of Wakeful Test (MWT)," "Multiple Sleep Latency Test (MSLT)," "Peripheral Arterial Tonometry (PAT)," "Physiological Measurements of Sleep as Used in **95805**," "Polysomnography," "Portable Recording," "Positive Airway Pressure (PAP)," "Remote," "Respiratory Airflow (Ventilation)," "Respiratory Analysis," "Respiratory Effort," "Respiratory (Thoracoabdominal) Movement," "Sleep Latency," "Sleep Staging," "Sleep Testing," "Total Sleep Time," and "Unattended." For example, Unattended: a technologist or qualified health-care professional is not physically present with the patient during the recording session.

Overutilization of 99214

The most common problem seen by Medicare is the overutilization of **99214** with documentation supporting a **99213**. PMC suggests that you review your records for the last several weeks/months and see if you believe you would withstand an audit of your documentation supporting your reported **99214** E/M visits. Pulmonologists generally report all levels of evaluation and management (E/M) of the established office/outpatient visit codes, with levels 4 and 5 being the most frequent.

2010 Medicare data show the following national percentage distribution for pulmonary medicine reporting established patient E/M codes compared to all the other medical specialties:

99211 0.77% (of 8,515,467)
99212 0.59% (of 19,291,310)
99213 1.81% (of 102,237,982)
99214 2.55% (of 79,920,491)
99215 2.84% (of 10,112,992)

It would be beneficial to review your E/M reporting for established patients in the office/outpatient setting to see if you and other providers in the practice have a distribution across all five codes (and check that the level is supported by medical necessity, ie, an ICD-9-CM code).

New COPD Measures Group

In addition to the existing two measures groups on Community Acquired Pneumonia and Asthma (ages 5 to 50 years of age), a new COPD Measures Group will be effective on January 1, 2012. This measures group will include the two existing COPD measures (unique #51 Spirometry evaluation and #52 Bronchodilator therapy) and two existing immunization/vaccine measures (#110 influenza and #111 pneumonia) and the new 2011 combined tobacco use: screening and cessation intervention, measure #226. The COPD measures group individual measures may also be reported individually. We do not expect any significant specification changes to the five individual performance measures. This will be significantly easier for pulmonologists to report in that usually only one or two G codes will replace the reporting of six to seven individual codes. Watch for updates in the weekly *Newsbrief*.

New Sleep Apnea Measures Group

For 2012, there is also a new sleep apnea measures group that will include assessment of sleep symptoms, severity assessment at initial diagnosis, positive airway pressure therapy prescribed, and assessment of adherence to positive airway pressure therapy. This sleep measures group is reportable through registry-based reporting only.

See the diagram of the historical improper payment rates for Medicare Fee-For-Service (facing page, bottom left).

New Telehealth, Smoking Cessation, and Critical Care

There are new smoking and tobacco cessation counseling codes: **G0436**, **G0437** for telehealth services for **asymptomatic** patients:

G0436 Smoking and tobacco cessation counseling visit for the asymptomatic patient; intermediate, greater than 3 minutes, up to 10 minutes

G0437 Smoking and tobacco cessation counseling visit for the asymptomatic patient; intensive, greater than 10 minutes

As a reminder, for critically ill patients and telehealth services, you would need to report Telehealth Consultation codes – **G0426, G0427** for an **initial** encounter and **G0406-G0408** for **follow-up** encounters. Existing **99291, 99292** were not approved for Telehealth reporting.

Pulmonary Rehabilitation

The Hospital Outpatient Payment Rule (OPPS-CMS-1525-FC) proposed a reduction from $62 to $38 for the bundled code, **G0424** Pulmonary Rehabilitation for patients with COPD. Other patients are reported with the timed, 15 minute **G0237**, **G0238** or group code, **G0239**. Robert DeMarco, MD, FCCP represented ACCP at the 8/24/11 meeting with CMS. A joint ACCP/ATS/AACVPR/AARC/NAMDRC letter was filed requesting that this proposed lowered payment be reconsidered. The Final rule published that **G0424** will be paid at $37 per hour.

New CPT Modifier 33 Preventive Services

In response to the Patient Protection and Affordable Care Act (ACA), health plans need to begin covering immunizations and preventive services without any cost sharing. Modifier **33** has been added to CPT to identify a service as preventive. If a CPT code descriptor identifies a code as preventive, such as preventive medicine counseling, the modifier should not be used.

Questions

For coding and practice management questions, contact ACCP staff, Marla Brichta at mbrichta@chestnet.org or at (847) 498-8364. ■

This Month in *CHEST*: Editor's Picks

BY DR. RICHARD S. IRWIN, MASTER FCCP

▶ **Lectin-Like Oxidized Low-Density Lipoprotein Receptor-1 Modulates Endothelial Apoptosis in Obstructive Sleep Apnea.**
By Dr. M. E. Akinnusi et al.

▶ **The Effect of Weight Loss and Exercise Training on Flow-Mediated Dilatation in Coronary Heart Disease: A Randomized Trial.**
By Dr. P. A. Ades et al.

▶ **Risk Factors for Tumor Recurrence in Patients With Early-Stage (Stage I and II) Non-small Cell Lung Cancer: Patient Selection Criteria for Adjuvant Chemotherapy According to the Seventh Edition TNM Classification.**
By Dr. R. Maeda et al.

▶ **Percutaneous Catheter Decompression in the Treatment of Elevated Intraabdominal Pressure.**
By Dr. M. L. Cheatham; and Ms. K. Safcsak.

POINT/COUNTERPOINT EDITORIAL

▶ **Should Lactate Clearance Be Substituted for Central Venous Oxygen Saturation as Goals of Early Severe Sepsis and Septic Shock Therapy?**
Yes. Dr. A. E. Jones.
No. Drs. E. P. Rivers; R. Elkin; and C. M. Cannon.

Critical Care Commentary

Postoperative Complications in Patients Undergoing Thoracic Surgery

Lung cancer is on the rise with the number of reported cases up from approximately 200,000 in 2007 to an estimated 220,000 in 2011. The advent of CT scanning has allowed more of these tumors to be diagnosed early. In turn, earlier detection of tumors has shown that they are more likely to be resectable. As such, more patients are undergoing pulmonary resections. Major complications occur in approximately 10% of patients undergoing pulmonary resections, and cardiopulmonary complications occur in more than 50% of these patients. Thus, it behooves the nonthoracic intensivist to become familiar with the common postoperative issues in patients who have undergone lung resection.

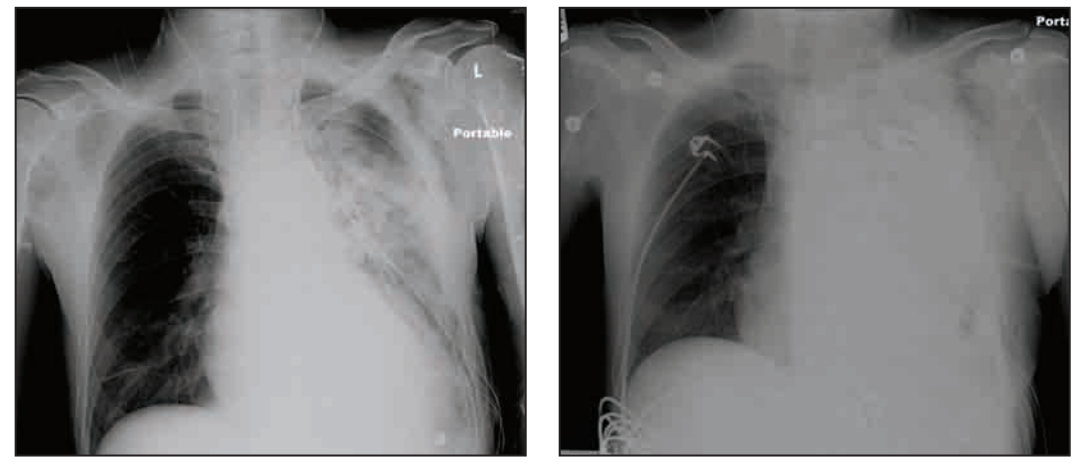


Fig 1. Left: Immediate postoperative chest radiograph after decortication. Right: Postoperative day 1 chest radiograph showing interval accumulation of hemothorax. Chest tube was noted to be clotted on reexploration.

Nonoperative Complications

Patients are prone to developing atelectasis and pneumonia after thoracic surgery. It is important that these patients are able to clear their own secretions. Three complementary approaches are used, which are adequate pain control; chest physiotherapy, including early mobility; and bronchoscopy. Pain control in a patient following thoracic surgery can be achieved with systemic opioids, nonsteroidal antiinflammatory agents, intercostal blocks, paravertebral blocks, epidural analgesia, and interpleural analgesics. A meta-analysis (Joshi et al. *Anesth Analg.* 2008;107[3]:1026) suggests that a thoracic epidural with local anesthetic plus an opioid is the most effective approach; however, thoracic paravertebral block with local anesthetic is a comparable alternative.

Regardless of the pain management strategy, the crucial element is the ability of patients to comfortably generate a good cough and clear their own secretions.

Chest physiotherapy, a vital adjunct in minimizing respiratory complications, includes incentive spirometry, coughing, chest percussion and vibration, and postural drainage. When performed by specialized therapists, the rates of pulmonary morbidity have been reported to improve from 15.5% to 4.7% (Novoa N et al. *Eur J Cardiothorac Surg.* 2011;40[1]:130).

However, patients must have adequate pain control in order to be motivated to undergo chest physiotherapy and be out of bed in a chair and ambulating on postoperative day one. For those patients who are unable to effectively clear their own secretions with noninvasive means, bronchoscopy may be warranted.

Postoperative acute lung injury (ALI) occurs in up to 7% of patients who undergo pulmonary resection, and the mortality rate is approaching 50%. Primary ALI occurs within 3 days of surgery, and its etiology is not well established. Risk factors are mostly unmodifiable and are thought to include preoperative alcohol abuse, large resection, transfusions, and increased intraoperative airway pressures. Secondary ALI occurs 3 days after surgery and results from identifiable causes such as pneumonia or aspiration. The primary perioperative risk factor that is modifiable is fluid management. Evidence shows that increased perioperative fluid

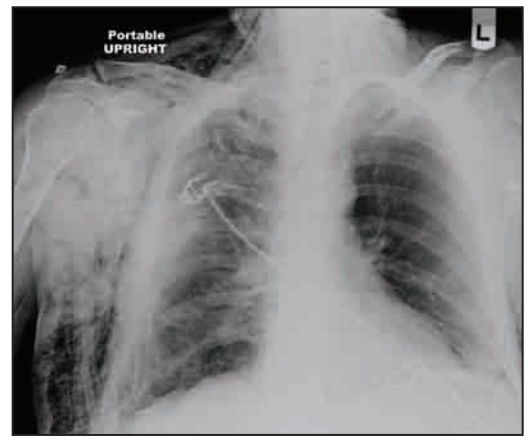


Fig 2. Subcutaneous emphysema after right-sided wedge resection.

administration increases the incidence of postoperative ALI.

One study (Alam N et al. *Ann Thorac Surg.* 2007;84[4]:1085) suggests that, for every 500-mL increase in perioperative fluids, there is an odds ratio of 1.17 for developing ALI. A proposed guideline suggests administering a maximum of 20 mL/kg of fluid in the first 24 h after surgery. Urine output of 0.5 mL/kg/h is acceptable in this period, and vasopressors may be used if tissue perfusion is inadequate (Slinger. *J Cardiothorac Vasc Anesth.* 1995;9[4]:442). Diuresis can be considered after the second postoperative day. Renal failure may occur from such fluid restriction, but this condition is usually reversible.

Atrial fibrillation is a common complication following pulmonary resections. The incidence increases with the greater extent of resection and the increasing age of the patient. Atrial fibrillation usually occurs within 2 to 3 days postoperatively and increases the hospital length of stay. The immediate therapeutic goal is rate control. Beta-blockade is usually the first-line treatment; however, calcium-channel blockers and digoxin have also been used. Good results have been observed with amiodarone, but some surgeons are wary of its use for the treatment of postoperative atrial fibrillation due to the risk of pulmonary toxicity in approximately 5% of patients. In fact, some surgeons do not use it in patients following a pneumonectomy for fear of harming the remaining lung.

Operative Complications

Bleeding is always a concern after surgery. The chest tube drainage system offers an excellent tool to monitor for postoperative hemorrhage. A rate of >100 mL/h for more than 2 h is cause for concern. Thick, red fluid is more concerning than thin, pink fluid. Checking a pleural fluid hematocrit can be performed; however, it is not indicated if clinical suspicion is high for postoperative bleeding. In fact, it may delay definitive treatment. Any coagulopathy should be corrected. Sometimes the chest tube may become clotted and stop draining effectively. In these cases, the radiograph will show a dramatic increase in pleural effusion. If there is no decrease in chest tube output or if a large effusion appears on chest radiograph despite functioning drainage catheters, the patient may need to undergo reexploration. (Fig 1).

Lobar torsion following thoracic surgery is a rare entity; however, the outcome may be fatal if left undiagnosed. Most cases involve the middle lobe following a right upper lobectomy. Patients can have fever, tachycardia, dyspnea, and diminished breath sounds. A high index of suspicion is required for this diagnosis. Chest radiograph shows a homogeneous consolidation in the superomedial right lung field. Bronchoscopy should be performed immediately, and if there is difficulty passing the scope into the middle lobe bronchus, the patient should be emergently reexplored.

Depending on the promptness of

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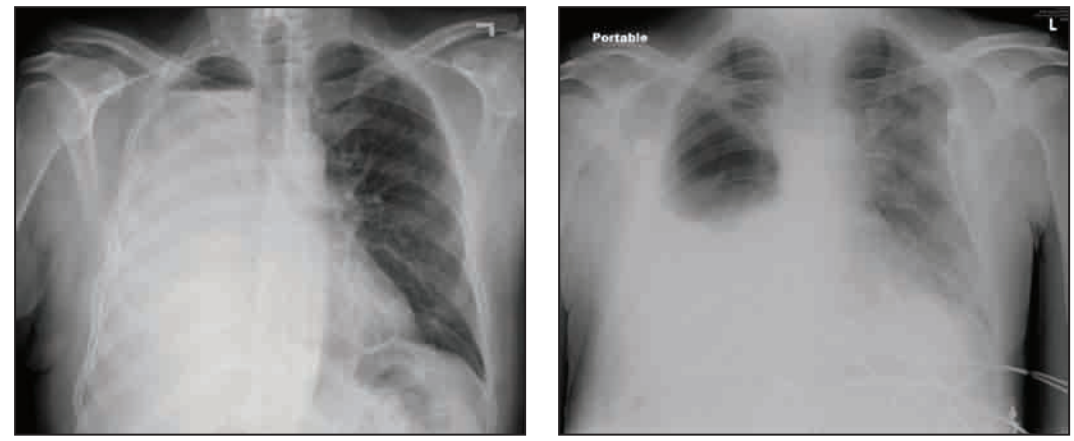

Images courtesy Dr. Dong-Seok Lee

Fig 3. Left: Four-week postoperative chest radiograph after right-sided pneumonectomy showing near opacification of right-sided hemithorax with sterile fluid. Right: Five-week postoperative chest radiograph showing a decrease in the amount of fluid in the right-sided hemithorax with concomitant aspiration-like changes on the contralateral side.

Continued from previous page

diagnosis, the patient may need a lobectomy.

Patients may have persistent air leaks, defined as an air leak lasting >7 days following pulmonary resection.

These air leaks can result from iatrogenic tears in the lung parenchyma or from parenchymal staple line dehiscence following a wedge resection. These patients may develop significant subcutaneous emphysema (Fig 2).

The development of subcutaneous emphysema signifies that the size of the leak is greater than the ability of the chest tube to evacuate the air, which is dependent on the chest tube management.

If the tube is placed on water seal when this occurs, it will need to be placed on suction. In contrast, if the chest tube is already on suction, the amount of suction will need to be increased (eg, from –20 to –40 cm H_2O of suction) or another chest tube may need to be inserted.

Management strategies for a continuous air leak differ depending on the size of the leak and the doctor's surgical mindset. If a patient is able to tolerate the chest tube placed on water seal, a Heimlich valve can be placed, the closed thoracotomy drainage system can be removed, and the leak can then be managed in an outpatient setting.

Other options include pleurodesis, blood patch, or reexploration to repair the leak.

Of particular concern is the persistent leak in a patient with a bronchial staple line, such as a patient who undergoes a lobectomy or pneumonectomy. In these patients, it is imperative to rule out the presence of a bronchopleural fistula. In a patient following pneumonectomy, a bronchopleural fistula may be seen with a decrease in air-fluid level on chest radiograph as the fluid leaks out of the pleural space (Fig 3).

Often, there is concomitant aspiration pneumonia on the contralateral side. This occurs as the fluid in the postpneumonectomy space empties into the contralateral airways via the fistula. In essence, the patient has "aspirated" his postpneumonectomy effusion. Should this be the case, a chest tube should be placed immediately. Bronchoscopic evaluation is then necessary to determine the presence of a bronchopleural fistula. These patients likely require reexploration and reclosure of the bronchial stump with a flap.

One final issue is management of the pleural space following a pneumonectomy. Some surgeons place a chest tube and either leave it on water seal or clamp the tube. Others do not place a chest tube at all; instead, they aspirate air from the pleural space at the end of the operation.

The key element to ensure is that the mediastinum is midline in the postoperative chest radiograph. If the patient subsequently becomes hemodynamically unstable, a tension hemithorax may be developing on the side of the lung removal. In this circumstance, air within the chest must be directly aspirated if there is no chest tube.

If a chest tube is in place but is clamped, the tube should be unclamped. However, if air removal does not improve the hemodynamic collapse, the rare complication of cardiac herniation should be considered, especially if an intrapericardial pneumonectomy was performed, and the patient taken to the operating room for immediate reduction.

Summary

It is important for pulmonologists, internists, and intensivists to be aware of postoperative issues in patients who undergo thoracic surgery. Although these physicians may not always be involved in the definitive treatment of certain complications, they remain a vital cog in the prompt diagnosis of problems encountered in the postoperative period. It is important to remember that the focus should not be on a single abnormal finding but rather on the whole picture (eg, clinical stability + tube output + chest radiograph) when managing these complications. ■

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BY PAUL MARKOWSKI, CAE

FROM THE EVP/CEO

Postcard From CHEST 2011

Dear ACCP members, staff, and other key stakeholders, Aloha from Honolulu, Hawaii!

► More than 300 chest medicine courses, sessions, and lectures attended by more than 4,900 registrants.

► Over 500 attendees interacting with presenters and obtaining information about how to replicate best practices at their own institutions as part of the new Centers of Excellence.

► Nine hundred guests enjoying traditional Hawaiian entertainment, including a lei greeting, Hawaiian cuisine, live music, and dancing, at the sold-out OneBreath Luau™ hosted by The CHEST Foundation.

There's only one meeting where all of these events could occur—aloha from a remarkably successful CHEST 2011, October 22-26, in Honolulu, Hawaii. And mahalo to the ACCP leaders, faculty, and staff who made this premier event possible, with a special thanks to Dr. Kevin Chan, FCCP, Chair of the CHEST 2011 Program Committee.

Additional CHEST 2011 Highlights

Registration for CHEST 2011 was up 5% from last year, particularly noteworthy given the meeting location and current financial climate. US and international registrations both exceeded the previous year.

A mobile-ready version of the meeting planner was available for attendees this year, and free Wi-Fi was accessible on-site.

Some of our leading medical experts visited several Hawaii hospitals, participating in grand rounds and critical care team debriefings, along with educating primary care physicians on COPD.

COURTESY ACCP

At the opening session, Dr. Chen G. Wang, FCCP, provided insights on how China addresses issues of lung health.

We expanded the global focus of the meeting to feature an international opening session and a chance to review unique cases from around the world during the first-ever global case reports session.

As part of the international opening session, Dr. Chen G. Wang, FCCP, provided insights on how China addresses issues of lung health and what the world can learn from China's experience. Additional speakers discussed tobacco and lung health from global- and population-based perspectives.

Newer members learned about ACCP leadership opportunities at the first-ever Affiliate and Leadership Reception. The "speed dating with a twist" format allowed affiliates to visit roundtables representing various leadership areas within the College, including the Board of Regents, ACCP Committees, NetWorks, US/Canadian Governors, International Regents, and The CHEST Foundation. At each table, relevant ACCP leaders shared their leadership experiences, explained how to get involved in their respective areas, and answered College-related questions.

New Research Presented

Autism and autistic spectrum disorders are currently diagnosed primarily through subjective observation of autistic behaviors. New research presented at CHEST 2011 suggests that a physical abnormality in the airway

may be a prominent indicator for autism and autistic spectrum disorders, making it a possible diagnostic marker for this disease. The potential association between autism and airway structure is intriguing; however, additional studies are needed to determine the genetic factors that may lead to airway abnormalities.

COURTESY ACCP

Nine hundred guests attended the sold-out OneBreath Luau™ hosted by The CHEST Foundation.

Sleeping less than 8 hours a night may be linked to weight gain in teens, according to a new study presented at CHEST 2011. In this study, obesity was linked to short sleep duration in teenage boys, with the fewest hours slept linked to the highest BMI levels.

Wish You Were Here

Unable to attend CHEST 2011 or stop by presentations of interest? You can access research that was presented in the October 2011 *CHEST* abstract supplement at http://chestjournal.chestpubs.org/.

More than 80% of the sessions presented at CHEST 2011 were recorded and are available for purchase. A significant discount is available for CHEST 2011 attendees. To receive the discount price, CHEST attendees should first register with OnlineEvent at http://onlineevent.com/OE_NewUser.aspx. Once registered, attendees can log in to receive the discounted price.

CHEST 2012

Looking ahead, we'll build on our commitments to integrating technology to enhance patient care and maximize the attendee experience, as well as cultivating our members as health-care leaders—themes for next year's annual meeting. See y'all in Atlanta for CHEST 2012.

Paul

P.S. Best wishes for a healthy and happy New Year from all of us at your ACCP.

COE and Touchdown Stations

On October 23, 2011, the American College of Chest Physicians hosted the presentations by the following 10 Centers of Clinical Excellence (COE) and three companies recognized for their support of the medical community. The inaugural event was visited by 500 to 700 CHEST 2011 attendees who were able to view the outstanding demonstrations and take home educational resources. The grand opening on Monday included a ribbon-cutting (Figure) by then ACCP President, Dr. David D. Gutterman, FCCP (center), with Dr. Ken Torrington, FCCP, Medical Director of the COE (right); and Dr. Sam Evans, ACCP Governor for Hawaii (left), assisting. Descriptions of the COE and touchdown stations will appear in the January and subsequent issues of *CHEST Physician*. If you wish to apply for participation in the COE for CHEST 2012, contact Dr. David H. Eubanks, FCCP(Hon), at deubanks@chestnet.org.

COURTESY ACCP

Dr. Evans, Dr. Gutterman, and Dr. Torrington (from left to right) cut the ribbon at the grand opening.

Centers of Excellence

- Hanuola ECMO Program of Hawaii
- Klingensmith HealthCare
- NorthShore University Health System
- Not One More Life
- Promise Hospital
- REMEO® Ventilation and Weaning Centers
- The Queen's Medical Center
- Tripler Army Medical Center & 13th Air Force
- UMass Memorial Medical Center
- University of Hawaii

Touchdown Stations

- Boehringer Ingelheim Pharmaceuticals, Inc.
- Genentech
- Novartis Pharmaceutical Corp. ■

Pulmonary Perspectives

Anterior Mediastinal Tumors: Biopsy—When, Why, How?

Mediastinal masses are relatively rare and encompass a wide variety of diseases from the purely benign to the extremely malignant. The three anatomic mediastinal compartments are clinically notable because specific lesions characteristically arise in certain locations, making the compartment of origin integral to the differential diagnosis. Greater than half of mediastinal masses occur in the anterior/superior compartment. Thymic neoplasms, lymphomas, thyroid masses, and germ cell tumors make up the classic differential. Management strategies for these tumors are diverse and depend strongly on the histologic diagnosis and extent of disease. The rarity of these masses has led to an unstructured approach to their workup, with a diversity of choices and indications for histologic diagnosis.

CT scan, MRI, and fluorodeoxyglucose positron emission tomography (FDG-PET) are the main imaging modalities used to evaluate anterior mediastinal masses. CT scanning provides a reliable evaluation of mediastinal anatomy and relationship of the lesion to adjacent structures. CT scan findings that help differentiate tumor histologic state are the presence of fat, cysts, and calcifications; contrast enhancement; invasion of adjacent structures; and associated mediastinal lymphadenopathy. Of these criteria, the presence of fat and associated mediastinal lymphadenopathy are the most useful. Presence of fat density on CT scan has a 57% sensitivity, 97% specificity, and 90% positive predictive value (PPV) for the diagnosis of a germ cell tumor, while associated mediastinal lymphadenopathy has a 75% sensitivity, 93% specificity, and 67% PPV for lymphoma (Totanarungroj et al. *J Med Assoc Thai*. 2010;93[4]:489).

While a definitive diagnosis can never be made by CT scan alone, there are constellations of CT findings that assist with diagnosis. Lymphomas are heterogeneous but rarely cystic. They may invade contiguous structures and have associated pleural or pericardial effusions. Only 5% of lymphomas occur solely in the mediastinum; therefore, extrathoracic lymphadenopathy is typically present. Teratomas can be smooth or lobulated but with smooth margins. Most are very heterogeneous with fluid, soft tissue, fat, and calcium. Seminomas are typically bulky, projecting out both sides of the mediastinum but rarely invade contiguous structures. They are homogeneous and have mild enhancement. Nonseminomatous germ cell tumors are large and inhomogeneous with areas of necrosis and hemorrhage, frequently invading or compressing adjacent structures, with resultant signs of obstruction. Substernal thyroid goiters can be traced in continuity to the cervical thyroid and have prolonged contrast enhancement. They can be definitively diagnosed by CT scan. Thymomas are typically well-defined and asymmetric, draping along one side of the heart. They can be homogeneous or heterogeneous based upon presence of hemorrhage, necrosis, and cyst formation, which are soft indicators for more invasive histologic status. Thymic carcinomas are similar in appearance to thymomas but have more irregular contour, necrotic or cystic components, heterogeneous enhancement, and evidence of great vessel invasion. They may also present with findings suggestive for metastatic spread.

MRI can provide additional information with regard to separation from bronchial and vascular structures. MRI is more accurate than CT scanning in assessing invasion into vessels and adjacent structures. T1-weighted images are best for anatomic assessment, while T2-weighted images are preferred for tissue characterization. FDG-PET can be useful in predicting grade of malignancy in thymic epithelial tumors and serves as a useful adjunct for assessment of extrathoracic lymphadenopathy in lymphomas.

The precise histologic state of an anterior mediastinal mass cannot be determined without tissue, but a reasonable diagnosis can frequently be made considering the radiographic findings, age of the patient, the presence or absence of symptoms, associated systemic disease, and biochemical markers. Thymoma accounts for 70% of anterior mediastinal masses in patients over 50 when one excludes the easily recognizable substernal goiters (Detterbeck et al. *Thorac Surg Clin*. 2011;21[1]:59). In this age group, one can be comfortable that a mass with the typical appearance of a thymoma is a thymoma. Conversely, thymomas are relatively uncommon in those younger than 20; clinical features are generally sufficient to guide treatment in this age group, but tissue is almost always required if the mass does not have the appearance of a mature teratoma. In the 20- to 40-year age group, the precise workup can be less clear. Thymomas in this age group are usually associated with myasthenia gravis or an indolent presentation. Lymphomas, on the other hand, typically present with B symptoms and a rapid progression of chest symptoms.

Since the introduction of video-assisted thoracoscopic surgery (VATS), the threshold for resection of mediastinal lesions without precise histologic diagnosis has been lowered. In patients who present with typical radiographic signs of mature teratomas, or in an older patient with a typical radiographic appearance for a thymoma, one can be confident in the diagnosis. In a recent survey of current practices among members of the European Society of Thoracic Surgeons, 91% of centers reported that they did not routinely look for a histologic diagnosis when presented with a small, resectable, encapsulated lesion, where the clinical presentation and CT scan characteristics are not suggestive of lymphoma (Ruffini et al. *J Thoracic Oncol*. 2011;6[3]:614). The presence of myasthenia gravis also helps in securing the diagnosis. Frozen section confirmation at the time of resection is difficult and not recommended unless unexpected intraoperative findings are encountered. There is no harm in performing a needle or incision biopsy of a small thymoma, if needed. The fear of tumor spread as a result of biopsy is not supported in the literature.

Making a precise diagnosis without tissue for poorly demarcated tumors of the anterior mediastinum is more difficult since large thymomas, thymic carcinomas, seminomas, nonseminomatous germ cell tumors, and lymphomas can have a similar radiographic appearance. Tissue diagnosis is particularly important if there is a high index of suspicion for a lymphoma or germ cell tumor, as these are not treated surgically. A variety of anterior mediastinum biopsy techniques are available, including CT-guided percutaneous needle biopsy, parasternal anterior mediastinotomy (Chamberlain procedure), VATS, and open surgical approaches. None of these procedures are universally accepted, either because of low diagnostic yield or associated morbidity. Core needle biopsy is preferred by some due to its ease, patient comfort, and low morbidity. Unfortunately, an accurate diagnosis by core biopsy is dependent upon good tissue retrieval without extensive necrosis, on-site cytologic examination, and an experienced pathologist. Immunohistochemistry enhances the diagnostic accuracy because of its utility in identifying and classifying lymphomas. In a recent comparison of core needle biopsy to mini-mediastinotomy in a series of 40 large unresectable anterior mediastinal masses, the diagnostic yield of mini-mediastinotomy was 85.7%, significantly higher than that of core needle biopsy at 41.7% (Fang et al. *Chin Med J (Engl)*. 2007;120[8]:675). Extensive necrosis was cited as most frequent reason for inability to make a diagnosis. Throughout the literature, sensitivity of needle biopsy is approximately 60%, while that of surgical biopsy is 90%. The perceived fear of pleural seeding during transthoracic core needle biopsy is also not substantiated in the literature. Many surgeons recommend surgical biopsy when histologic status is needed. In the recent European Society of Thoracic Surgeons survey, most respondents stated that they preferred surgical biopsy by VATS or anterior mediastinotomy when histologic status is required. During anterior mediastinotomy, efforts should be made to avoid the internal mammary artery and to stay out of the pleural space. These biopsies are typically done under general anesthesia but have been reported in awake patients. VATS approaches are preferred by many, and awake biopsy by this approach has also been reported (Pompeo et al. *Thorac Surg Clin*. 2010;20[2]:225). There are rare occasions when minimally invasive approaches are insufficient to obtain adequate tissue, and sternotomy or thoracotomy is indicated. This is most common with nodular sclerosing Hodgkin's disease, due to its dense fibrotic capsule.

Tumors of the anterior mediastinum generate substantial interest, typically due to their large size and the diversity of the diagnosis and associated treatment plans. The threshold for biopsy prior to definitive resection is based on numerous factors, including size, encapsulation, respectability, patient age, and associated clinical scenario. Since resectability is an important component of this decision, appropriate diagnostic workup is best determined by a team that includes a thoracic surgeon. Mode of biopsy is highly dependent on institutional expertise, but surgical biopsy provides the greatest chance for adequate diagnosis with minimal associated morbidity and mortality. ■

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Supreme Court Takes Up Health Reform

BY MARY ELLEN SCHNEIDER
Elsevier Global Medical News

The U.S. Supreme Court has agreed to hear arguments on the constitutionality of the Affordable Care Act, with a decision likely to come in June.

On Nov. 14, the high court announced that it would consider arguments related to a well-publicized challenge to the health reform law that was originally filed in Florida. The Florida case, which was brought by a coalition of Republican attorneys general and governors from 26 states along with the National Federation of Independent Business, asserted that the individual mandate, which requires all Americans to have health insurance, violates the Constitution.

The coalition of states also objected to the law's broad expansion of Medicaid. They argued that requiring states to invest billions of dollars in an enlarged Medicaid program violated state sovereignty.

The Supreme Court has agreed to hear arguments related to the constitutionality of both the individual mandate and the Medicaid expansion. The justices also said that if the individual mandate is declared unconstitutional, they will then consider whether the law can stand without it or must be struck down completely.

Opponents of the Affordable Care Act cheered the Supreme Court's decision to accept the case.

Greg Abbott, the attorney general for Texas, which is part of the case being considered by the high court, said the court's decision to accept the case means the law is just one step closer to being tossed out.

But White House officials also think they can win the case. "We know the Affordable Care Act is constitutional and are confident the Supreme Court will agree," White House communications director Dan Pfeiffer said in a statement.

Families USA, a consumer advocacy group and supporter of the ACA, issued a statement saying it is "surprised and troubled" that the Supreme Court chose to review the expansion of Medicaid.

"It is particularly disingenuous for the states bringing this case to object to this expansion of Medicaid as 'coercive,' because the Affordable Care Act specifies that between 90% and 100% of the costs of this expansion will be paid for by the federal government," Families USA executive director Ron Pollack said in a statement.

'STRIKING DOWN THIS MEDICAID EXPANSION WOULD JEOPARDIZE HEALTH CARE FOR MILLIONS OF LOW-INCOME AMERICANS.'

"Striking down this Medicaid expansion would jeopardize health care for millions of low-income Americans at a time when they can least afford it," he said.

The first decision in the Florida case came in January when U.S. District Court Judge Roger Vinson ruled that the individual mandate was unconstitutional and voided the entire law. However, he did not agree with the states' argument that the law's Medicaid expansion was unconstitutional.

Next, the 11th Circuit Court of Appeals in Atlanta took up the case, agreeing with Judge Vinson that the individual mandate violated the Commerce Clause of the U.S. Constitution.

But in a 2-1 ruling on Aug. 12, the appeals court ruled that the individual mandate could be separated from the rest of the Affordable Care Act, allowing that law to stand.

Both the federal government and the plaintiffs in the Florida suit petitioned the Supreme Court to take up the case.

Court watchers had expected the justices to consider the Affordable Care Act in its current term since there have been conflicting rulings from the appeals courts on the law.

While the 11th Circuit ruled against the individual mandate, other appeals courts have dismissed challenges to the law. ■

Final 2012 Fee Cut Is 27%, Not 29%

BY ALICIA AULT
Elsevier Global Medical News

If current law stands, physician fees will be cut by 27% in 2012, not the 29% originally projected, according to the final payment rule issued Nov. 1 by the Centers for Medicare and Medicaid Services.

The slight decrease is due to lower-than-expected Medicare cost growth, CMS officials said in a statement. Unless Congress steps in, the reduction will go into effect Jan. 1 as mandated by Medicare's Sustainable Growth Rate (SGR) formula.

Both President Obama, in his budget, and CMS officials have called for an overhaul of the SGR. The agency repeated that call with the issuing of the fee rule. "This payment rate cut would have dire consequences that should not be allowed to happen," CMS Administrator Donald Berwick said in a statement. "We need a permanent SGR fix to solve this problem once and for all."

"Almost every year for more than a decade, doctors have faced this annual threat and the Congress has in turn acted to temporarily prevent these deep reductions from taking effect," Kathleen Sebelius, Health and Human Services secretary, said in a statement. "We have not and will not let deep cuts to doctors' payments occur. The Obama administration is 100% committed to fixing the flawed Medicare payment system and protecting Medicare beneficiaries' access to doctors."

The American Medical Association also urged Congress – yet again – to fix the SGR. Physician payments are so low that "there is a 20% gap between Medicare payment updates and the cost of caring for seniors," AMA President Peter W. Carmel said in a statement.

Under the final rule, Medicare will issue some $80 billion in payments next year, according to CMS estimates.

In addition to addressing physicians' fees, the final rule includes many cost-cutting and efficiency-oriented provisions. For instance, the CMS is expanding its look at codes that may be overvalued. Previously, the agency focused on high-cost codes in cardiology and radiology. In 2012, it will take a broader look, focusing on codes in each specialty that lead to the highest Medicare expenses.

The agency is also taking a knife to payments for imaging services by going after multiple images taken of the same patient at the same practice on the same day. The CMS had proposed a 50% cut in the professional component; the final rule makes a 25% reduction.

The final rule made several changes to the electronic health records incentive program and the Physician Quality Reporting System. For EHRs, physicians now have the option to submit data through several different portals. The agency also more closely aligned the PQRS requirements with the EHR meaningful use requirements.

The rule also establishes measures to be used in the future to pay physicians for higher quality and more efficient care. Payment adjustments will begin in 2015 and be applied to all physicians by 2017.

Under the rule, the so-called "value-based modifier" will use the PQRS core set (which focuses on cardiovascular conditions) and the EHR Incentive Program measures (which focus on several chronic conditions and preventive measures). Payments to group practices will be based on the core set of the Group Practice Reporting Option measures and measures of preventable hospital admissions for heart failure and COPD.

The cost measures will be both total per capita cost and per capita cost for selected conditions including COPD, heart failure, and coronary artery disease.

For provisions that are open to comment, the CMS will accept comments until Jan. 3, 2012, and then respond in the 2013 fee rule. ■

COMMENTARY

Dr. Stuart Garay, FCCP, comments: Any physician that left a condition untreated for a decade would be viewed as completely irresponsible. It is widely agreed that the SGR formula is flawed. Yet for a decade, Congress has failed to fix the problem. The final payment rule issued by CMS on Nov. 1 stated that there will be a 27% reduction in Medicare physician fees, instead of the originally projected 29%.

The smaller reduction in Medicare rates is attributed to lower Medicare utilization. So the impact of the cut could potentially be greater. As utilization decreases, so does reimbursement into the health care system, which further reduces physicians' income. Now add the reduced Medicare rates. Don't fret! Congress has the last word. We will know by the end of the year what the final outcome will be. Stay tuned!

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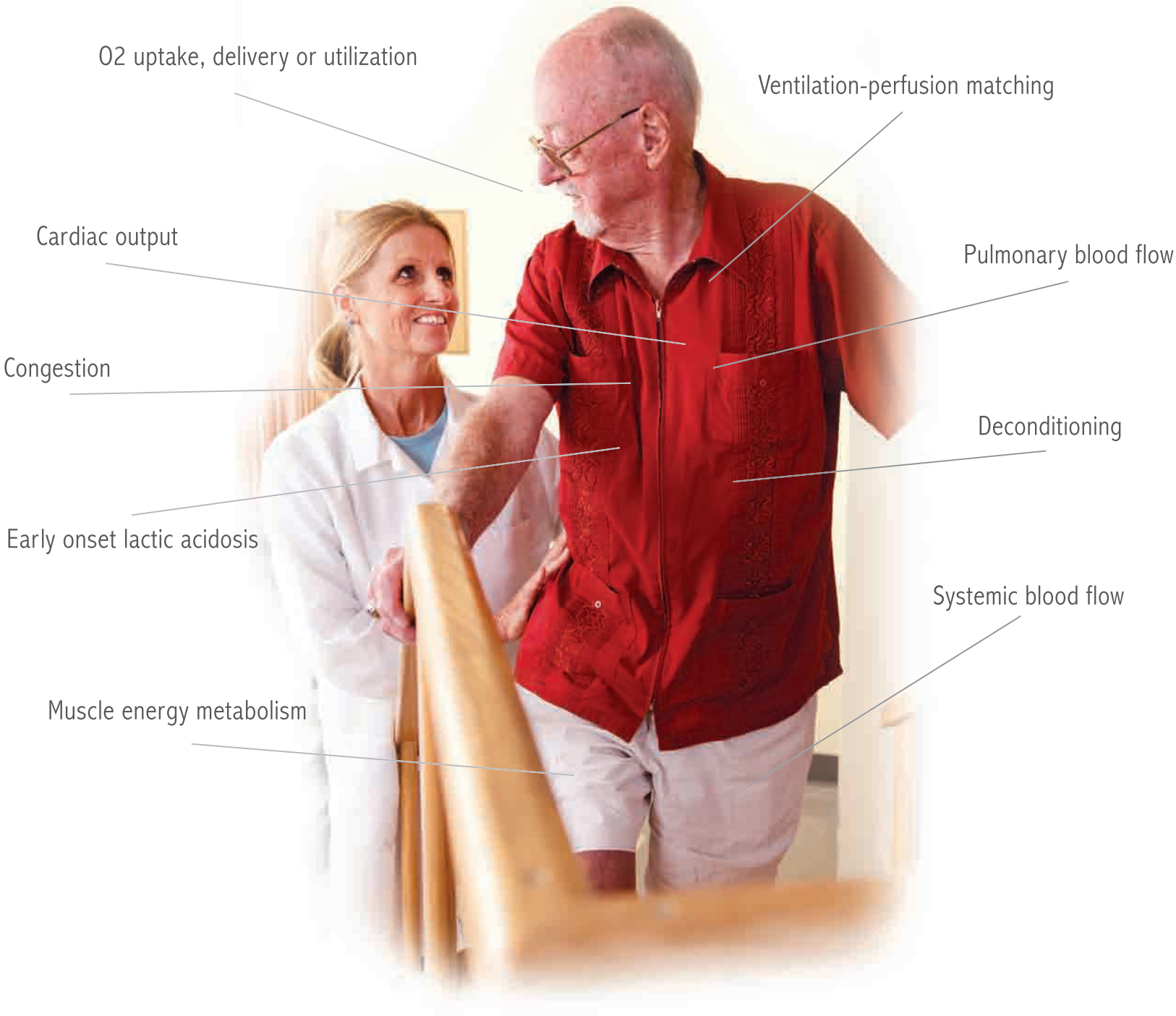

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