VOL. 6 • NO. 11 • NOVEMBER 2011

CHEST Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

DOUG BRUNK/ELSEVIER GLOBAL MEDICAL NEWS

The lower airways of children with autism have doubled branches, Dr. Barbara A. Stewart, FCCP, reported at CHEST 2011 in Honolulu.

Airway Abnormality Discovered in Autism

BY DOUG BRUNK
Elsevier Global Medical News

The presence of extra bronchial passageways in children may be a marker for autism and autism spectrum disorders, results from a novel study demonstrated.

"Autism continues to remain underdiagnosed or missed altogether, unrecognized and undiagnosed because appropriate tools for screening for autism have not been available," lead investigator Dr. Barbara A. Stewart, FCCP, said during an interview in advance of the annual meeting of the American College of Chest Physicians, where the study was presented. "Until now, there has been no objective evidence for autism spectrum disorder."

Dr. Stewart of Nemours Children's Clinic in Pensacola, Fla., conducted bronchoscopic evaluations in 49 children younger than age 18 years who had autism or autism spectrum disorder and were seen in a pulmonary clinic with a diagnosis of cough that was unresponsive to therapy. She noticed that although the airways of the children initially appeared normal, the lower airway had doubled branches, or "doublets."

"Another way to think of this is systematic doubling of airways in the lower airways," Dr. Stewart explained. "When airways divide beyond the first generation, they typically branch like a tree, with one branch on one side and one on the other. A doublet occurs when there are twin branches that come off together instead of one, which are exactly symmetrical, in each of the lower locations that can be seen."

Because of a lack of uniformity in nomenclature in the medical literature, Dr. Stewart said that it's difficult to determine if doublets have been previously identified, let alone studied. "There are no known studies in the literature attempting to define or even speculate on a function, purpose, role, [or] significance of the 'double takeoff' airway anomaly," she said.

See **Airway** • *page 2*

X-Ray Screening Doesn't Prevent Lung Ca Deaths

Study bolsters CT screening results.

BY SHARON WORCESTER
Elsevier Global Medical News

Compared with usual care, the use of annual chest radiographs as a screening tool for lung cancer did not reduce lung cancer mortality in the large, randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.

The results dovetail with findings published earlier this year from the NLST (National Lung Screening Trial), which demonstrated a 20% mortality advantage with computed tomography screening vs. chest radiograph screening (N. Engl. J. Med. 2011;365:395-409), according to Dr. Martin M. Oken of the University of Minnesota, Minneapolis, and his colleagues from the PLCO (Prostate, Lung, Colorectal, and Ovarian) Cancer Screening Trial Project Team.

It follows that CT screening also has a similar advantage over usual care, the investigators said.

In the PLCO trial, the cumulative incidence rates of lung cancer after 13 years of follow-up were 20.1 and 19.2 per 10,000 person-years in the 77,445 trial participants randomized to receive screening with annual chest radiographs and the 77,456 participants assigned to usual care, respectively (relative risk, 1.05). The number of lung cancer deaths was 1,213 in the radiograph group and 1,230 in the usual care group, for cumulative incidence rates of 14.0 and 14.2 per 10,000 person-years, respectively (RR, 0.99), they reported online in the Oct. 26 issue of JAMA.

The lung cancer mortality relative risks were 0.94 for never smokers, 1.02 for former

See **Lung Cancer** • *page 3*

INSIDE

Lower Radiation Dose Better in NSCLC

BY NEIL OSTERWEIL
Elsevier Global Medical News

MIAMI BEACH – Less turned out to be better in a large clinical trial comparing radiation doses in patients treated with radiation and chemotherapy for stage III non–small cell lung cancer, investigators reported at the annual meeting of the American Society for Radiation Oncology.

The median overall survival rate at 1 year was 81% for patients treated with standard-dose (60 Gy) radiation, compared with 70.4% for those who received the high dose (74 Gy), according to preliminary findings from the radiation-dose arm of the ongoing phase III Radiation Therapy Oncology Group (RTOG) 0617 trial. The respective median survival rates were 21.7 months and 20.7 months ($P = .02$).

A planned interim analysis from the trial showed that the radiation comparison had crossed the prespecified boundary for futility, and the high-dose arm was stopped in June 2011, Dr. Jeffrey Bradley

See **Radiation** • *page 3*

CHEST Physician
60 Columbia Rd.,
Bldg. B, 2nd flr.
Morristown, NJ 07960

CHANGE SERVICE REQUESTED

Presorted Standard
U.S. Postage
PAID
Permit No. 384
Lebanon Jct. KY

Autism Anomaly

Airway • *from page 1*

She speculated that children with doublets may have higher airway resistance, which "might be why the population of children with autism spectrum disorder are not truly athletic people."

Although the potential association between autism and airway structure is intriguing, Dr. Stewart emphasized the preliminary nature of the findings. "That there is such a compelling correlation between a perplexing bronchial anomaly and a seemingly unrelated condition such as autism begs further study," she said. "This discovery needs to be validated by much larger–scale investigations than my own."

She noted that research into neurodevelopmental processes, including autism and autism spectrum disorder, and anatomical anomalies such as doublets in the bronchi "should and will be accelerated." She also expressed the hope that "likely less-invasive alternatives to bronchoscopy will be discovered in the near future to justify identification of airway anomalies as a diagnostic tool for autism."

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

IN THIS ISSUE

CHEST PHYSICIAN Is Online

CHEST PHYSICIAN is available on the Web at www.chestnet.org/accp/chest-physician.

Asthma Measures, Outcomes Unrelated

BY MARY ANN MOON
Elsevier Global Medical News

Hospital compliance with the Children's Asthma Care set of process measures did not correlate with asthma patients' clinical outcomes in a study of more than 37,000 asthma patients who were admitted to 30 U.S. children's hospitals, a new study found.

Because compliance with these process measures was not associated with improved outcomes, it "cannot serve as a means to evaluate and compare the quality of care provided for patients admitted with asthma exacerbations," said Dr. Rustin B. Morse of Phoenix Children's Hospital and the University of Arizona, Phoenix, and his associates.

The Joint Commission considers the Children's Asthma Care (CAC) measure set to be an "accountability measure," appropriate for use in determining accreditation, public reporting of hospital performance, and pay for performance. But the findings of this study instead suggest that the measures do not meet Joint Commission criteria for accountability measures and should be "reconsidered," Dr. Morse and his colleagues said.

They assessed time trends in compliance with the CAC measure set using data on a random sample of 37,267 pediatric inpatients with 45,499 admissions for asthma exacerbations during a 33-month period at 30 freestanding children's hospitals across the country.

The CAC measure set includes three measures: whether patients received asthma relievers on admission (CAC-1), whether they received systemic corticosteroids on admission (CAC-2), and whether they were discharged with a complete home management plan of care (CAC-3). Compliance is measured quarterly by a review of the medical records of a random sample of patients.

Compliance with CAC-1 and CAC-2 was quite high, exceeding 95% in all but 1 of the 11 quarters assessed, and was consistent across hospitals. Because there were so few cases of poor compliance, no analysis could be performed.

In contrast, mean CAC-3 compliance was only 41% during the first three quarters of the study and improved to 73% in the final three quarters.

This allowed an analysis of the relationship between CAC-3 compliance and clinical outcomes. No significant association was found between compliance and improved outcomes at 7, 30, or 90 days after discharge, the investigators said (JAMA 2011;306:1454-60). ■

VITALS

Major Finding: Compliance with two of the three CAC process measures was so high that no analysis could be performed to assess whether it correlated with patient outcomes, and compliance with the third measure did not correlate with patient outcomes.

Data Source: A cross-sectional study assessing 30 U.S. children's hospitals' compliance with the CAC measures set in a sample of 37,267 pediatric asthma patients seen during a 33-month period.

Disclosures: One of Dr. Morse's associates reported ties to the Robert Wood Johnson Foundation, the National Institute of Allergy and Infectious Diseases, the Child Health Corporation of America, and the Pediatric Research in Inpatient Settings Network; two reported grants from the Agency for Healthcare Research and Quality.

COMMENTARY

Dr. Burt Lesnick, FCCP, comments: Most clinicians believe that providing a written, personalized asthma management plan at the time of discharge after an asthma exacerbation is an important component of care. It helps identify asthma triggers, which medications to use for maintenance, which to use for rescue, what to do in case of an exacerbation, and who to contact for additional care. The management plans, however, are not always appropriate to the level of literacy of the family or even in the primary language spoken in the house. Furthermore, in some institutions, the plan is part of a comprehensive education program, while in others only the bare minimum of a written management plan is provided. When a comprehensive education program is utilized, the cultural competency of the instructor may affect the family's adherence to the care plan. It is important that case management confirms the medication prescribed at time of discharge will actually be covered by the family's insurance plan. The authors have concluded that the asthma management plan is a poor proxy for the global process of educating a patient's family and a smooth hand-off to primary care. We must seek additional metrics that may be more specific. We should not necessarily discard the asthma management plan as an important tool in that care continuum.

AMERICAN COLLEGE OF CHEST PHYSICIANS®

AMERICAN COLLEGE OF CHEST PHYSICIANS
Editor in Chief Paul A. Selecky, M.D., FCCP
Deputy Editor in Chief W. Michael Alberts, MD, FCCP
President David D. Gutterman, MD, FCCP
Executive Vice President and CEO Paul A. Markowski, CAE
Senior Vice President, Communications Stephen J. Welch
Manager, Editorial Resources Pamela L. Goorsky
Medical Copy Editor II Peggy E. Perona, R.D.

Section Editors
Marilyn G. Foreman, M.D., FCCP - **Pulmonary Perspectives Editor**
Loren J. Harris, M.D., FCCP - **Pulmonary Perspectives Deputy Editor**
Neil Halpern, M.D., FCCP - **Critical Care Commentary**
James Parish, M.D., FCCP - **Sleep Strategies**

EDITORIAL ADVISORY BOARD
Joseph Barney, M.D., FCCP, Alabama
Jun Chiong, M.D., FCCP, California
Stephen Field, M.D., FCCP, Calgary
Richard Fischel, M.D., FCCP, California
Stuart M. Garay, M.D., FCCP, New York
Carl Kaplan, M.D., FCCP, Missouri
Burt Lesnick, M.D., FCCP, Georgia
Darcy D. Marciniuk, M.D., FCCP, Saskatchewan
Jeana O'Brien, M.D., FCCP, Texas
Marcos I. Restrepo, M.D., MSc, FCCP, Texas
Nirupam Singh, M.D., FCCP, California

E-mail: chestphysiciannews@chestnet.org

CHEST PHYSICIAN

CHEST PHYSICIAN, the newspaper of the American College of Chest Physicians, provides cutting-edge reports from clinical meetings, FDA coverage, clinical trial results, expert commentary, and reporting on the business and politics of chest medicine. Each issue also provides material exclusive to the members of the American College of Chest Physicians. Content for **CHEST PHYSICIAN** is provided by International Medical News Group, an Elsevier company. Content for NEWS FROM THE COLLEGE is provided by the American College of Chest Physicians.

The statements and opinions expressed in **CHEST PHYSICIAN** do not necessarily reflect those of the American College of Chest Physicians, or of its officers, regents, members, and employees, or those of the Publisher. The American College of Chest Physicians, its officers, regents, members, and employees, and Elsevier Inc. do not assume responsibility for damages, loss, or claims of any kind arising from or related to the information contained in this publication, including any claims related to products, drugs, or services mentioned herein.

Address Changes: Fax changes of address (with old mailing label) to 973-290-8245.

POSTMASTER: Send change of address (with old mailing label) to CHEST PHYSICIAN, 60 B Columbia Rd., 2nd flr., Morristown, NJ 07960.

CHEST PHYSICIAN (ISSN 1558-6200) is published monthly for the American College of Chest Physicians by Elsevier Inc., 60 B Columbia Rd., 2nd flr., Morristown, NJ 07960, 973-290-8200, fax 973-290-8250.

IMNG MEDICAL MEDIA

IMNG SOCIETY PARTNERS, A DIVISION OF IMNG MEDICAL MEDIA
President, IMNG Medical Media Alan J. Imhoff
Director, IMNG Society Partners Mark Branca
Editor in Chief Mary Jo M. Dales
Executive Editors Denise Fulton, Kathy Scarbeck
Managing Editor Leanne Sullivan

Audience Development Manager Barbara Cavallaro, 973-290-8253, b.cavallaro@elsevier.com
Executive Director, Operations Jim Chicca
Director, Production and Manufacturing Yvonne Evans Struss
Production Manager Judi Sheffer
Creative Director Louise A. Koenig
Display Advertising Manager The Walchli Tauber Group: 443-512-8899, fax 443-512-8909, greg.pessagno@wt-group.com

ADVERTISING OFFICES 60 B Columbia Rd., 2nd flr., Morristown, NJ 07960, 973-290-8200, fax 973-290-8250
CLASSIFIED ADVERTISING OFFICES The Walchli Tauber Group, 2225 Old Emmorton Rd., Suite 201, Bel Air, MD 21015, 443-512-8899
EDITORIAL OFFICES 5635 Fishers Lane, Suite 6000, Rockville, MD 20852, 240-221-4500, fax 240-221-2541

Radiography No Help

Lung Cancer • *from page 1*

smokers, and 0.99 for current smokers, and for men and women, respectively, the mortality risks were 1.02 and 0.92.

In a subset of 15,183 intervention patients and 15,138 usual care patients from the PLCO trial who would have met eligibility criteria for the NLST, which was initiated 9 years after the PLCO trial, the cumulative lung cancer incidence rates per 10,000 person-years through 6 years of follow-up were 60.6 and 60.8 in the groups, respectively, the investigators also noted.

Cumulative lung cancer mortality rates in that subset of patients were 36.1 and 38.3 per 10,000 person-years in the radiograph and usual care groups, respectively (RR, 0.94).

"The corresponding [relative risk] for the total PLCO cohort at 6 years was 1.02 for lung cancer incidence and 0.91 for lung cancer mortality," the investigators said.

The PLCO findings, which were published simultaneously with their presentation at CHEST 2011, not only facilitate interpretation of the NLST results, but also "provide important information about the benefits and harms of annual chest radiographic screening," the investigators said, noting that although there were some modest differences between the PLCO and NLST cohorts, "it seems reasonable to consider the chest radiograph vs. usual care comparison in the NLST-eligible cohort in the PLCO to be an adequate surrogate for such a comparison with NLST" (JAMA 2011 Oct. 26 [doi:10.1001/jama.2011.1591]).

"As such, the 20% mortality benefit of low-dose spiral CT vs. chest radiograph observed in NLST is likely a good approximation for the mortality benefit that must have been observed of low-dose spiral CT vs. usual care if this latter group had been added to NLST," they said.

PLCO participants were adults aged 55-74 years who were randomly assigned between November 1993 and July 2001 to receive annual screening with posterior-anterior view chest radiographs for 4 years or usual care, which included usual medical care with no interventions.

Adherence to the assigned screening protocol was 86.6% at baseline and 79%-84% at years 1-3. In the usual care group, an estimated 11% (the "contamination rate") underwent chest radiograph screening.

The primary treatment for lung cancer in both groups was similar: The predominant therapy for stage I and II non–small cell lung cancers was resection without chemotherapy, and for stage III or IV non–small cell lung cancers, the predominant therapy was chemotherapy without resection, the investigators noted.

'THERE IS NOT A SUBSTANTIAL LUNG CANCER MORTALITY BENEFIT FROM LUNG CANCER SCREENING WITH 4 ANNUAL CHEST RADIOGRAPHS.'

"The randomized groups in the PLCO were comparable at baseline, there was relatively high screening adherence in the intervention group and low contamination in the usual care group, and the treatment distributions across the groups were similar. Therefore, these findings provide good evidence that there is not a substantial lung cancer mortality benefit from lung cancer screening with 4 annual chest radiographs," the investigators wrote,

The findings of the NSLT and the PLCO trial complement each other, Dr. Harold C. Sox said in an editorial that accompanied the report (JAMA 2011 Oct. 26 [doi:10.1001/jama.2011.1609]).

"The PLCO has now demonstrated that screening with annual chest radiography does not lower lung cancer mortality relative to usual care," he said, posing the question of whether it is possible, then, to infer that screening with low-dose CT, which in the NSLT was linked with a survival advantage compared with chest radiography, reduces lung cancer morality relative to usual care.

"The PLCO lung cancer study result provides convincing evidence that lung cancer screening with chest radiography is not effective. The study is important for putting this question to rest and providing strong empirical grounds for comparing low-dose CT to a real-world alternative: usual care," noted Dr. Sox.

As for how the evidence will translate into policy and practice, that is a question that depends on analyses that have not yet been completed. "The PLCO trial is another important step, confirming expectations rather than setting new ones," he said. ■

VITALS

Major Finding: The number of lung cancer deaths was 1,213 in the group randomized to receive screening with annual chest radiographs and 1,230 in the usual care group, for cumulative incidence rates of 14.0 and 14.2 per 10,000 person-years, respectively (relative risk, 0.99).

Data Source: The randomized, controlled Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.

Disclosures: The PLCO Cancer Screening Trial was funded by the National Cancer Institute (NCI) and supported by contracts from the NCI's Division of Cancer Prevention and by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics NCI, National Institutes of Health, Department of Health and Human Services. Several authors disclosed potential conflicts of interest, including financial relationships with a number of pharmaceutical companies; the complete list of disclosures is provided in the JAMA article.

COMMENTARY

Dr. W. Michael Alberts, FCCP, comments: The negative results of the lung cancer portion of the PLCO Cancer Screening Trial directly complement the positive results of the NLST. The PLCO trial confirmed the widely held notion that an annual CXR confers no mortality benefit over usual care. The next obvious question was studied in the NLST (i.e., if an annual CXR is not helpful, how about low-dose spiral CT?). For those in a defined high-risk group, low-dose spiral CT did confer a mortality benefit when compared with an annual CXR and therefore usual care, as well. The PLCO trial and the NLST were huge trials that produced important results that justified the effort.

Higher Dose Didn't Prolong Life

Radiation • *from page 1*

from Washington University in St. Louis, reported.

"I think this changes practice: If [cancer centers] weren't using 60 Gray before, perhaps they should go back to using 60 Gray, because it does not appear that a higher dose is better," Dr. Bradley commented at the ASTRO meeting.

Dr. Tim R. Williams, from the Lynn Cancer Institute at Boca Raton (Fla.) Regional Hospital, the immediate-past chairman of ASTRO, noted that his center has used high-dose radiation in stage III non–small cell lung cancer (NSCLC) patients for about 5 years.

Although practice patterns vary, it's likely that many treatment centers currently use the higher dose, Dr. Williams said.

In RTOG 0617, a total of 500 patients with stage IIIA/IIIB NSCLC were scheduled for randomization to one of four arms in a 2 x 2 factorial design with patients assigned to receive either 74 Gy or 60 Gy radiation with or without cetuximab (Erbitux), on a background chemotherapy regimen of weekly paclitaxel (45 mg/m^2) and carboplatin (titrated to an area-under-the-curve of 2).

The radiation was delivered in 2 Gy fractions over 30-37 fractions.

The analysis was performed on 426 patients who had been enrolled in the study before June 17, 2011.

Seeking to understand why the higher radiation dose was not better – the investigators had originally hypothesized that 74 Gy would result in a 7-month improvement in overall survival vs. 64 Gy – they performed univariate analyses, and found that significant predictors for better outcomes included continuous therapy, nonsquamous histology, and, female gender. In multivariate analysis, radiation dose (60 Gy vs. 74 Gy) was associated with a hazard ratio for overall survival of 1.48 (P = .038), nonsquamous histology versus squamous was associated with an HR of 1.52 (P = .025), and gross or internal tumor volume had a small but significant HR of 1.002 (P = .011).

Dr. Benjamin Movsas, chair of radiation oncology at the Henry Ford Health System in Detroit, the invited discussant, said that "as of 2011, level I evidence demonstrates no role for dose escalation in stage III non–small cell lung cancer."

He noted that although there were small differences between the radiation dose groups in terms of tumor histology, gross tumor volume, and other factors, they were not large enough to explain the differences in outcomes.

Citing the advice of his late father, also a physician, Dr. Movsas reminded the audience that "More is not always better."

The RTOG 0617 trial is continuing with patients assigned to 60 Gy radiation only, with the goal of evaluating the secondary study end point of overall survival of patients with or without cetuximab added to concurrent chemoradiotherapy. ■

VITALS

Major Finding: Median overall survival among patients with stage III NSCLC treated with chemotherapy was 20.7 months with high-dose radiation (74 Gy) vs. 21.7 months with standard-dose radiation (60 Gy; P = .02).

Data Source: 426 patients enrolled in the randomized controlled RTOG 0617 trial.

Disclosures: The RTOG 0617 trial is supported by grants from the U.S. National Cancer Institute, with additional support from Bristol-Myers Squibb and ImClone. Dr. Bradley and Dr. Williams had no disclosures. Dr. Movsas disclosed departmental research support from Varian and Philips. He also has served as a chair of an RTOG committee, but was not involved in the 0617 study.

COMMENTARY

Dr. W. Michael Alberts, FCCP, comments: As mentioned in the article, "more is not always better." Another applicable saying might be "that's why they play the game." One would think that if you could safely administer 74 Gy to the tumor (as compared to 60 Gy), a superior outcome would be the result. On the contrary, this RTOG trial proved the converse. Randomized clinical trials are necessary to confirm (or refute) our clinical opinions.

Dronedarone Upped CV Events in Permanent A-Fib

BY ELIZABETH MECHCATIE
Elsevier Global Medical News

A significant increase in cardiovascular events in patients with permanent atrial fibrillation who are taking dronedarone in the PALLAS trial has led the drug's manufacturer to suspend the phase IIIb study.

The Food and Drug Administration approved dronedarone in 2009 for reducing the risk of cardiovascular hospitalization in patients with paroxysmal or persistent AF or atrial flutter (AFL), with a recent episode of AF/AFL and associated cardiovascular risk factors who are in sinus rhythm or who will be cardioverted. (In the European Union, it is indicated for clinically stable adults with a history of nonpermanent AF or with current nonpermanent AF, to prevent the recurrence of AF or to lower the ventricular rate.)

PALLAS (Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy) was discontinued for enrolled patients with permanent AF.

The international phase IIIb study compared dronedarone 400 mg twice daily (the approved dose) to placebo in about 3,000 patients with permanent AF, who were over age 65 and had comorbidities such as previous myocardial infarction, documented coronary artery disease, previous stroke, symptomatic heart failure, or diabetes. Patients with New York Heart Association class IV or unstable NYHA class III heart failure were excluded.

The company stopped the study in response to recommendations made by the study's operations and data monitoring committees, after a significant increase in cardiovascular events was observed among the patients in the dronedarone arm, according to the statement.

In the statement, the study's co–principal investigator, Dr. Stuart Connolly, director of the cardiology division and professor of medicine at McMaster University, Hamilton, Ont., said that the committee members were "very disappointed to discover that the hypothesis that dronedarone would improve major outcomes for this high-risk patient population has been refuted."

Patients enrolled in PALLAS had permanent AF and were more likely to have advanced vascular disease than patients in whom the drug is currently indicated, who have intermittent AF and most often do not have advanced vascular disease, Dr. Connolly said in an interview.

"The results of PALLAS do not bear directly on the patients on dronedarone for the approved indication," he noted. "So it is reasonable to continue those patients on dronedarone, and I would expect that they will still benefit from it in terms of reduced cardiovascular hospitalization."

About 70% of the patients enrolled in PALLAS had had permanent AF for more than 2 years, and about 70% had NYHA class I-III heart failure at baseline, which the Sanofi statement listed as other differences between these patients and the patients enrolled in the ATHENA study that supported the currently approved indication. (In the ATHENA study, fewer than 30% of patients had NYHA class I-III heart failure and none had permanent AF, the statement said.)

This is not the first indication that dronedarone may not be suitable for sicker patients. Its label already includes a black box warning that says the drug is contraindicated in patients with NYHA class IV heart failure or NYHA class II-III heart failure with a recent decompensation requiring hospitalization or referral to a heart failure clinic. This warning was based on the results of another dronedarone study that was stopped early – the ANDROMEDA study (Antiarrhythmic Trial With Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease) – which found that mortality was increased among such patients who were given dronedarone, when compared with placebo.

Dr. Connolly said he has received grant support and consulting and lecture fees from Sanofi. ■

COMMENTARY

Dr. Jun Chiong, FCCP, comments: The prevalence of atrial fibrillation is increasing with the graying of America. To date, no long-term agent has been proved to be safe for atrial fibrillation. This recent study proves that antiarrhythmic agent use should be monitored regularly and should be stopped or tapered as patients' symptoms improve or the atrial fibrillation becomes permanent, as will eventually be the case in most patients.

Poor Outcomes Terminate Triple Therapy in IPF Trial

BY HEIDI SPLETE
Elsevier Global Medical News

The National Heart, Lung, and Blood Institute has halted the triple-drug therapy arm of a treatment trial for idiopathic pulmonary fibrosis because of poor outcomes, according to a statement issued by the National Institutes of Health.

Interim data from the study indicated that patients with idiopathic pulmonary fibrosis (IPF) who received a combined therapy of prednisone, azathioprine, and *N*-acetylcysteine (NAC) had no improvement in lung function, compared with a placebo group.

In addition, compared with the placebo group, the treatment group had significantly higher rates of death (11% vs. 1%), hospitalization (29% vs. 8%), and serious adverse events (31% vs. 9%).

The study, known as PANTHER-IPF (Prednisone, Azathioprine, and *N*-acetylcysteine: A Study That Evaluates Response in Idiopathic Pulmonary Fibrosis), was designed to evaluate the effectiveness of a triple-therapy regimen in slowing disease progression and improving lung function in patients with moderate to severe IPF. The average age of the study participants at enrollment was 68 years.

"This combination therapy is widely used in patients with IPF but has not previously been studied in direct comparison to a placebo for all three drugs," Dr. Susan B. Shurin, acting director of the NHLBI, noted in a statement.

Patients in the other two treatment arms who are receiving NAC alone or a placebo will continue with their designated treatment protocols, which are scheduled to last up to 60 weeks, according to the statement released by the National Institutes of Health.

The researchers began enrolling patients in 2009. Completion of the first phase of the study with the two remaining treatment arms is expected by 2013.

More details about the trial are available online at www.clinicaltrials.gov.

The study was supported by National Institutes of Health and the Cowlin Family Fund at Chicago Community Trust. The NAC and matching placebo treatments were donated by Zambon; study funds were used to purchase the prednisone, azathioprine, and matching placebos. ■

ACIP Considers Recommending PCV13 for Adults

BY HEIDI SPLETE
Elsevier Global Medical News

The Food and Drug Administration is expected to approve the 13-valent pneumococcal conjugate vaccine (PCV13) for use in adults aged 50 years and older, but before it becomes widely used for that age group, more research is needed on immune response in adults, the herd effect produced by vaccinating children, and the overall preventable disease burden among adults.

That was the conclusion of the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices, which discussed whether they should expand the recommendations for the vaccine at a recent meeting. Currently, PCV13 is recommended for all children aged 2-59 months and up to 71 months, if underlying conditions put the child at higher risk.

"Licensure will be based on immunogenicity data only, comparing the immune response of PCV13 to PPSV23," said Dr. Michael Marcy, chair of the pneumococcal vaccines working group. Published immunogenicity studies have shown noninferior immune responses in adults after one dose of PCV13, compared to PPSV23 for all common serotypes.

"The models show that PCV13 in adults could be highly cost effective," said Tamara Pilishvili, who is a CDC representative on the pneumococcal vaccines working group. However, the cost-effectiveness model assumes indirect effects of PCV13 on nonbacteremic pneumonia. If PCV13 proved ineffective against nonbacteremic pneumonia, there would be less support to recommend the vaccine for use in adults.

Factors favoring the use of PCV13 in adults include the potential to reduce a large burden of adult disease, improving on the limited acceptance of PPSV23 in the adult population, and capitalizing on the success of the PCV13 vaccine in children, Ms. Pilishvili said.

Factors weighing against the use of PCV13 in adults include the potential for the herd effects from vaccinating children to curtail the overall impact of vaccinating the adult population. Few data back the efficacy of the vaccine to prevent pneumonia in adults. There also are challenges and costs involved in attempting to expand vaccine coverage in the adult population, she noted.

The working group will evaluate new data as they become available, including results from a randomized, controlled trial of the efficacy of PCV13 against community-acquired pneumonia in adults aged 65 years and older from the Study Evaluating a 13-Valent Pneumococcal Conjugate Vaccine in Adults (CAPITA). Additional immunogenicity data will also be analyzed from a phase III trial of adults aged 18-49 years, as well as adults at increased risk for pneumococcal disease.

The proposed indication for PCV13 is for the prevention of disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F.

Ms. Pilishvili and Dr. Marcy reported that they had no financial conflicts of interest. ■

USAGE

- **To reduce the development of drug-resistant bacteria and maintain the effectiveness of TEFLARO® and other antibacterial drugs, TEFLARO should be used to treat only CABP or ABSSSI that are proven or strongly suspected to be caused by susceptible bacteria.**
- **When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.**

INDICATIONS

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

IMPORTANT SAFETY INFORMATION

Contraindications

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

Please see additional Important Safety Information throughout and brief summary of Prescribing Information on last page of this advertisement.

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

Teflaro®
(ceftaroline fosamil) for injection
600 mg • 400 mg

INDICATIONS AND USAGE

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

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Hypersensitivity Reactions

- Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and serious skin reactions have been reported with beta-lactam antibacterials. Before therapy with TEFLARO is instituted, careful inquiry about previous hypersensitivity reactions to other cephalosporins, penicillins, or carbapenems should be made. If this product is to be given to a penicillin- or other beta-lactam-allergic patient, caution should be exercised because cross sensitivity among beta-lactam antibacterial agents has been clearly established.
- If an allergic reaction to TEFLARO occurs, the drug should be discontinued. Serious acute hypersensitivity (anaphylactic) reactions require emergency treatment with epinephrine and other emergency measures that may include airway management, oxygen, intravenous fluids, antihistamines, corticosteroids, and vasopressors as clinically indicated.

Clostridium difficile-associated Diarrhea

- *Clostridium difficile*-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial agents, including TEFLARO, and may range in severity from mild diarrhea to fatal colitis. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents. If CDAD is suspected or confirmed, antibacterials not directed against *C. difficile* should be discontinued, if possible.

Broad-spectrum coverage for treating CABP and ABSSSI

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

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

CABP | **ABSSSI**

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

IMPORTANT SAFETY INFORMATION

Direct Coombs' Test Seroconversion

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

Development of Drug-Resistant Bacteria

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

Please see additional Important Safety Information throughout and brief summary of Prescribing Information on last page of this advertisement.

Teflaro®
(ceftaroline fosamil) for injection
600 mg • 400 mg

Demonstrated efficacy in CABP

TEFLARO CABP Study Designs[1,3]

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

Study population: 1231 adults with a diagnosis of CABP

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

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

TEFLARO Study Populations

Day 4 Population (mITT)*		A microbiological intent-to-treat population (mITT population) containing only subjects with a confirmed bacterial pathogen at baseline.
Test of Cure (TOC) Populations†		
MITT	Modified Intent-to-treat	All randomized subjects who received any amount of study drug.
MITTE	Modified Intent-to-treat Efficacy	All subjects in the MITT population who were in PORT Risk Class III or IV at baseline.
CE	Clinically Evaluable	All subjects in the MITTE population who demonstrated sufficient adherence to the protocol. Sufficient adherence is defined as patients who met the minimal disease criteria for CABP and for whom sufficient information regarding the CABP was available to determine the patient's outcome.
ME	Microbiologically Evaluable	All subjects in the CE population who had at least one typical bacterial pathogen identified at baseline from an appropriate microbiological specimen (eg, blood, sputum, or pleural fluid).

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

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

INDICATION AND USAGE

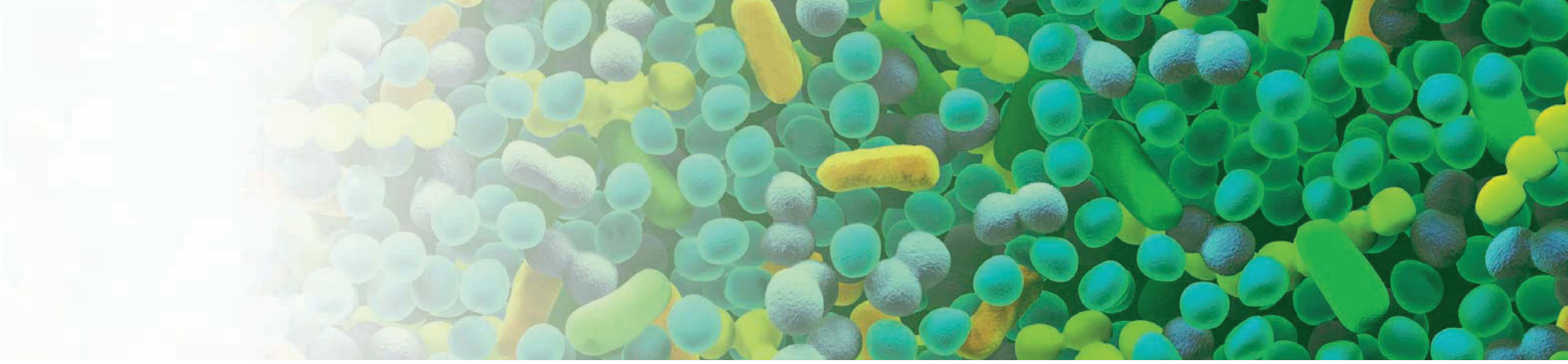
- TEFLARO is indicated for the treatment of **community-acquired bacterial pneumonia (CABP)** caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Streptococcus pneumoniae* (including cases with concurrent bacteremia), *Staphylococcus aureus* (methicillin-susceptible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

IMPORTANT SAFETY INFORMATION

Adverse Reactions

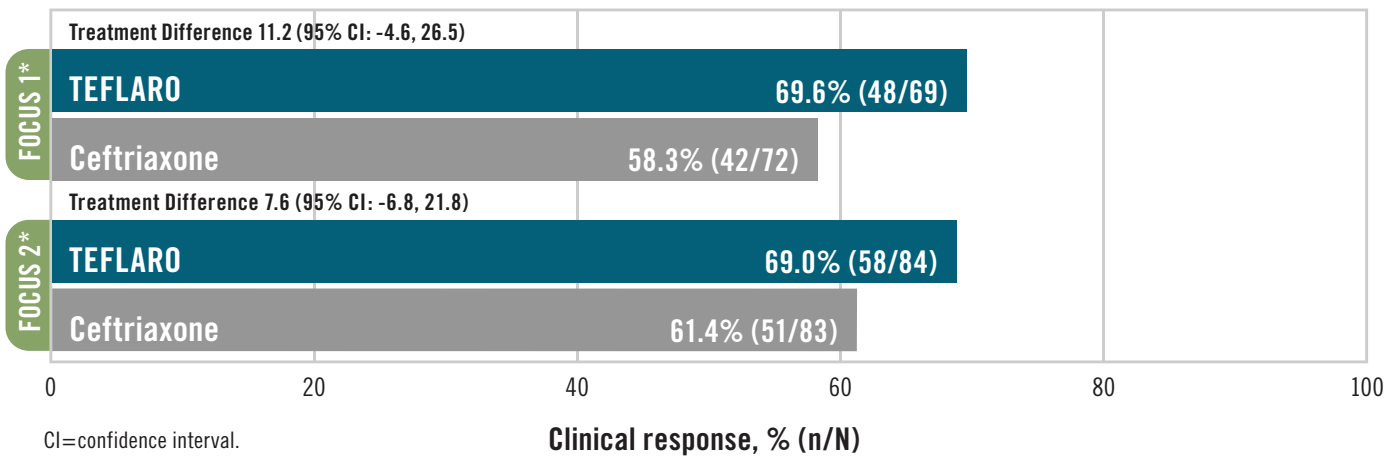
- In the four pooled Phase 3 clinical trials, serious adverse events occurred in 98/1300 (7.5%) of patients receiving TEFLARO and 100/1297 (7.7%) of patients receiving comparator drugs. Treatment discontinuation due to adverse events occurred in 35/1300 (2.7%) of patients receiving TEFLARO and 48/1297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

Please see additional Important Safety Information throughout and brief summary of Prescribing Information on last page of this advertisement.



CABP

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

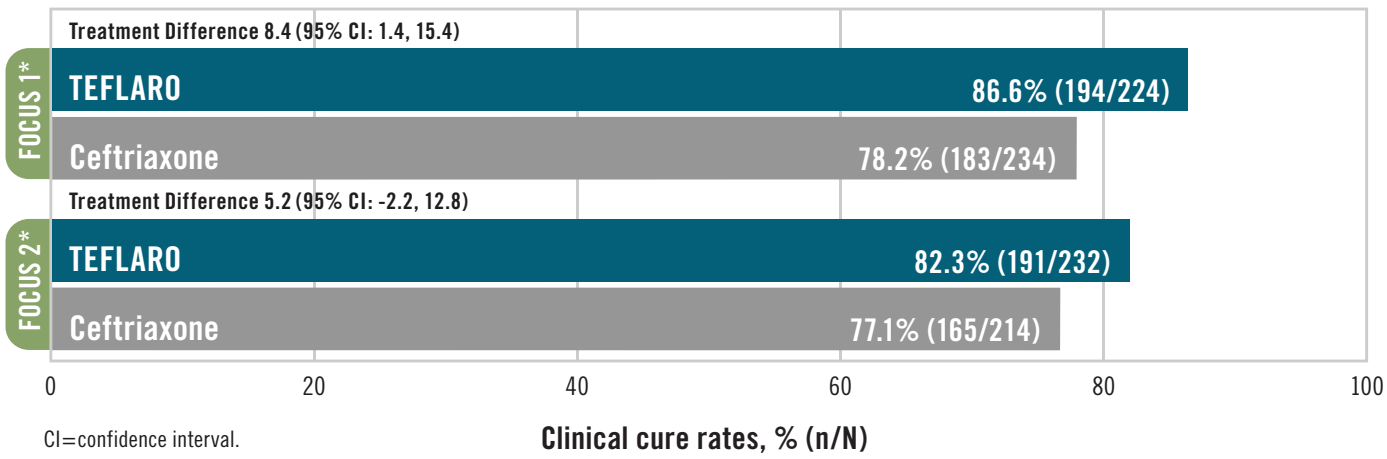


CI=confidence interval.

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

CABP

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



CI=confidence interval.

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

Patients with known or suspected MRSA were excluded from both trials.

*FOCUS=Ce**f**tar**o**line **C**ommunity-Acquired Pne**u**monia Trial v**s** Ceftriaxone in Hospital Patients. FOCUS 1=CABP Trial 1, FOCUS 2=CABP Trial 2.

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

IMPORTANT SAFETY INFORMATION

Drug Interactions

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

Teflaro®
(ceftaroline fosamil) for injection
600 mg • 400 mg

Demonstrated efficacy in ABSSSI

TEFLARO ABSSSI Study Design[1,3]

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

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

Comparative agents: TEFLARO – 600 mg administered IV over 1 hour every 12 hours for 5-14 days;
Vancomycin plus aztreonam – 1 g vancomycin administered IV over 1 hour followed by 1 g aztreonam administered IV over 1 hour every 12 hours for 5-14 days

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

TEFLARO Study Populations

Day 3 Population*		The analysis evaluated patients with lesion size ≥75 cm^2 and having one of the following infection types: – Major abscess with ≥5 cm of surrounding erythema – Wound infection – Deep/extensive cellulitis
Test of Cure (TOC) Populations†		
MITT	Modified Intent-to-treat	All randomized subjects who received any amount of study drug.
CE	Clinically Evaluable	Patients in the MITT population who demonstrated sufficient adherence to the protocol. Sufficient adherence is defined as patients who met the minimal clinical disease criteria for cSSSI and all evaluability criteria, including subjects who received at least the pre-specified minimal amount of the intended dose and duration of study drug therapy, for which sufficient information regarding the cSSSI site is available to determine the subject's outcome, and for which there were no confounding factors that interfered with the assessment of that outcome.
ME	Microbiologically Evaluable	This population consists of a subset of subjects from the CE population who had at least one bacterial pathogen identified from a blood culture or culture of an adequate microbiological sample obtained from the cSSSI site at baseline and who had susceptibility testing performed on at least one of the isolated baseline pathogens.

*To evaluate the treatment effect of ceftaroline, an analysis was conducted in 797 patients with ABSSSI (such as deep/extensive cellulitis or a wound infection [surgical or traumatic]) for whom the treatment effect of antibacterials may be supported by historical evidence. This analysis evaluated responder rates based on achieving both cessation of lesion spread and absence of fever on Trial Day 3.

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

INDICATION AND USAGE

- TEFLARO is indicated for the treatment of **acute bacterial skin and skin structure infections (ABSSSI)** caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*.
- To reduce the development of drug-resistant bacteria and maintain the effectiveness of TEFLARO and other antibacterial drugs, TEFLARO should be used to treat only ABSSSI that is proven or strongly suspected to be caused by susceptible bacteria.

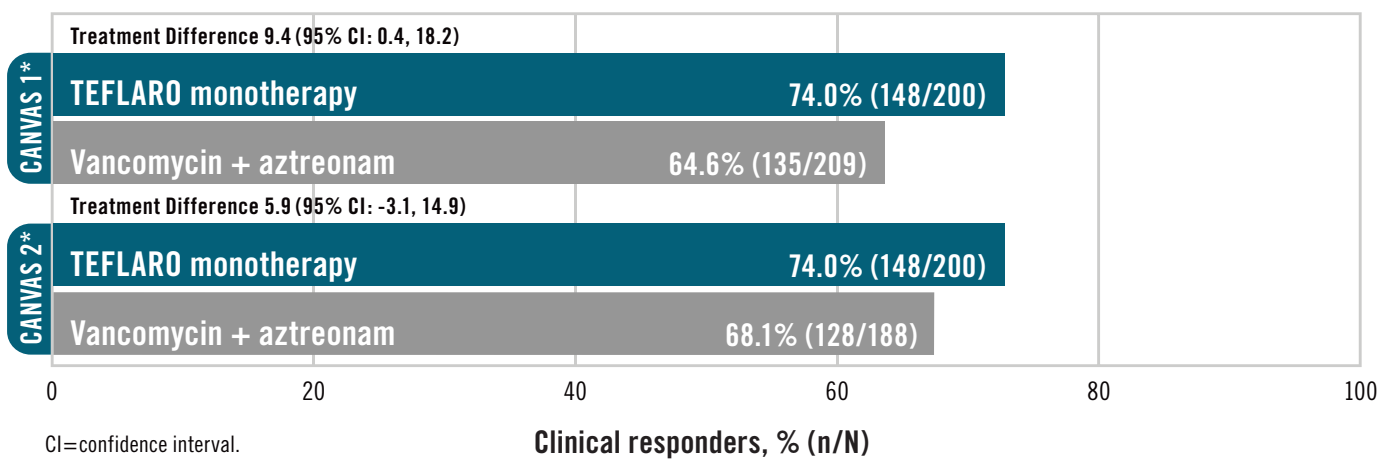
IMPORTANT SAFETY INFORMATION

Use in Specific Populations

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

ABSSSI

TEFLARO Demonstrated Clinical Response at Day 3 in Acute Bacterial Skin and Skin Structure Infections[1]



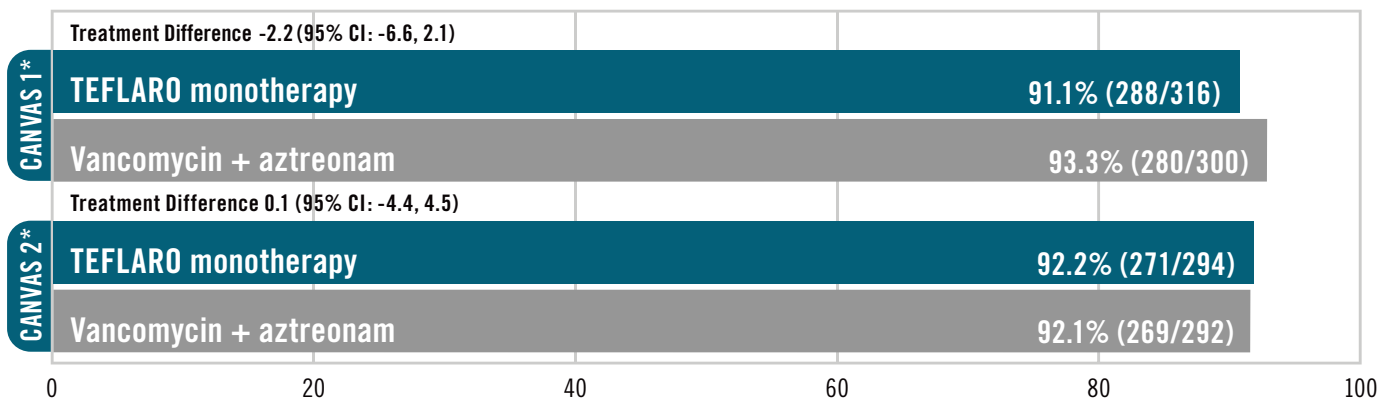
CI=confidence interval.

Clinical responders, % (n/N)

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

ABSSSI

TEFLARO Demonstrated Efficacy at TOC† (CE) in Acute Bacterial Skin and Skin Structure Infections[1]



CI=confidence interval.

Clinical cure rates, % (n/N)

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

*CANVAS=**C**eft**a**rolin**e** **v**s V**a**ncomycin in **S**kin and Skin Structure Infection. CANVAS 1=ABSSSI Trial 1, CANVAS 2=ABSSSI Trial 2.

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

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

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

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

Teflaro®
(ceftaroline fosamil) for injection
600 mg • 400 mg

‘On-Off’ Sleep Switches Shed Light on Brain Disorders

BY BETSY BATES
Elsevier Global Medical News

SAN DIEGO – A series of “on-off” switches regulates sleep, clarifying many of the mechanisms underlying narcolepsy, cataplexy, and REM sleep behavior disorder, according to Dr. Clifford B. Saper.

The states of sleep and wakefulnesss, as well as the states of rapid eye movement and non-REM sleep, can best be understood as “flip-flop” mechanisms of brain circuitry, somewhat akin to light switches, said Dr. Saper, who is professor of neurology and neuroscience at Harvard Medical School and head of the department of neurology at Beth Israel Deaconess Medical Center in Boston.

“Each side inhibits the other” in an ascending arousal pathway to the cortex, facilitating rapid transitions from one state to the other, he said.

Normally, human beings spend 99% of the 24-hour day either fully awake or fully asleep; just 1% of the time is spent transitioning between the two states. This cycle is due to the on-off switch that regulates arousal and sleep, Dr. Saper explained at the annual meeting of the American Neurological Association.

“One of the problems with a flip-flop switch is that it has a tendency, sometimes, to fall into the wrong position too easily. One can imagine driving down a boring road and flipping into the wrong state and suddenly being asleep behind the wheel of a car,” he said.

To prevent such an occurrence, the brain stabilizes wakefulness by the use of orexins, or hypocretins, which are neuropeptides produced by excitatory neurons in the lateral region of the hypothalamus.

Narcolepsy, in which patients do fall asleep essentially at the “flip of a switch,” is the result of a single neurotransmitter deficit in sleep’s “master switch,” the ventrolateral preoptic nucleus, Dr. Saper explained.

A similar “flip-flop” switch regulates the normally rapid transition between REM and non-REM (slow-wave) sleep, he said.

The development of REM sleep behavior disorder (a condition in which patients make jerky physical motions as they act out dreams during sleep) and cataplexy – atonic lapses in muscle control while in a waking state – are opposites on a spectrum, but both are indicative of a triggering of the on-off mechanism at an inappropriate point in the cycle.

Early markers of Parkinson’s disease have been found in REM sleep behavior disorder patients.

DR. SAPER

Of great interest to Dr. Saper is an evolving apparent link between the development of REM sleep behavior disorder in young adulthood and later development of Parkinson’s disease. It’s been shown that Parkinson’s disease develops in about half of patients with REM sleep behavior disorder within 12 years of the onset of the sleep disorder.

He noted that Dr. Ronald B. Postuma and his associates at Montreal General Hospital have identified several early markers of Parkinson’s disease that are commonly found in idiopathic REM sleep behavior disorder patients. These early markers include difficulties with performing visual and olfactory discrimination tasks and subthreshold but low scores on the Unified Parkinson’s Disease Rating Scale.

The connection has led some researchers to suspect that synucleinopathies such as Parkinson’s disease and dementia with Lewy bodies may begin at the brainstem level of the locus coeruleus or the subcoeruleus complex and slowly progress in an ascending pathway to the basal ganglia over years or decades. This theory may offer the possibility of introducing neuroprotective therapy to stop that progression.

Dr. Saper reported that he has no financial disclosures relevant to his presentation. ■

Combined TPA/DNase Aids in Pleural Infection

BY JEFFREY S. EISENBERG
Elsevier Global Medical News

Intrapleural therapy with combined recombinant tissue plasminogen activator and DNase improved fluid drainage in patients with pleural infection, led to fewer surgical referrals, and reduced the length of hospital stays, according to results of the second Multicenter Intrapleural Sepsis Trial (MIST 2). However, neither agent when used alone was more effective than placebo.

VITALS

Major Finding: Pleural opacity was 29.5% in the group treated with a combination of TPA and DNase, compared with 17.2% in the placebo group, a significant difference.

Data Source: MIST 2, a double-blind, double-dummy factorial randomized trial of 210 patients with pleural infection.

Disclosures: The study was funded by an unrestricted educational grant from Roche UK to the University of Oxford and by grants from the Oxford Biomedical Research Centre Programme and the U.K. Medical Research Council. Dr. Davies and Dr. Wrightston disclosed receiving lecture fees from ResMed UK and Boehringer Ingelheim UK, respectively.

Pleural infection affects more than 65,000 patients annually in the United States and United Kingdom, with a mortality rate of 10%-20%. Standard therapy typically consists of antibiotics and tube drainage of the infected fluid and surgery when sepsis and infected fluid are not effectively controlled.

Although the large first Multicenter Intrapleural Sepsis Trial (MIST1) showed no benefit of intrapleural streptokinase, the strong clinical and observational support for the use of fibrinolytic agents inspired MIST2 using a different direct-acting fibrinolytic agent – recombinant TPA – coupled to the use of recombinant DNase (to decrease viscosity due to extracellular bacterial DNA and inhibit biofilm formation), which has shown to be effective in animal studies.

To test these purported benefits, Dr. Najib M. Rahiman of the University of Oxford and colleagues conducted a double-blind, double-dummy factorial randomized trial of 210 patients with pleural infection at 11 centers in the United Kingdom between December 2005 and November 2008 (N. Engl. J. Med. 2011; 365:518-26). They randomized patients to receive one of four treatments: TPA plus DNase, DNase plus placebo, TPA plus placebo, and double placebo. The primary analysis included 193 patients, with 51 receiving double placebo, 48 receiving TPA only, 46 receiving DNase only, and 48 receiving both agents.

The dose of DNase (Pulmozyme, Roche) was 5 mg, and the dose of TPA (Actilyse, Boehringer Ingelheim) was 10 mg. Intrapleural medications were given twice daily for 3 days, and each administration was followed by drain clamping to permit the study drug to remain in the pleural space for 1 hour. Pulmozyme is approved by the Food and Drug Administration for the treatment of cystic fibrosis; Actilyse (marketed as Activase in the United States) is FDA-approved for use in acute ischemic stroke.

Baseline characteristics, including age, sex, percent of hemothorax occupied with pleural fluid, and characteristics of the infection and physiological status of the pleural fluid were not significantly different among the four groups.

The mean decrease in pleural opacity, the primary end point, was 29.5% in the TPA-DNase group between days 1 and 7. This was clinically and statistically significant, compared with 17.2% in the placebo group. There was no significant improvement in the primary outcome compared with the placebo when using TPA alone (17.2% decrease) or DNase alone (14.7%).

Researchers also looked at several secondary end points and found that:

► The frequency of referral for surgery at 3 months was 2 of 48 patients (4%) in the TPA-DNase group vs. 8 of 51 patients (16%) in the placebo group, 18 of 46 patients (39%) in the DNase only group, and 3 out of 48 patients (6%) in the TPA group. All referrals were due to clinical evidence of worsening infection.

► Hospital stays on average were 11.8 days for the TPA-DNase group vs. 16.5 days, 28.2 days, and 24.8 days for the TPA, Dnase, and placebo groups, respectively.

► Mortality rates were not significantly different for all four study groups at 3 months and 12 months. At 3 months, mortality rates were 2 of 50 patients (4%) in the placebo group, 4 of 48 patients (8%) in the TPA-DNase group, 4 of 48 patients (8%) in the TPA group, and 6 of 46 (13%) in the DNase group. At 12 months, mortality rates were 4 of 48 (8%) patients in the placebo group, 5 of 47 patients (11%) in the combination group, 5 of 46 patients (11%) in the TPA group, and 9 of 45 patients (20%) in the DNase group.

► Thoracic surgery and deaths due to pleural infection were evenly distributed across all four groups.

These results show that combined intrapleural TPA and DNase therapy improves the drainage of pleural fluid in patients with pleural infection and may improve the natural history of infection, including reduced hospital stays and the need for thoracic surgery.

"This combined treatment may therefore be useful in patients in whom standard medical management has failed and thoracic surgery is not a treatment option," the researchers said. " If confirmed in further studies, our results will inform the choice of intrapleural adjuvant therapy for pleural infection and improve the management of this disorder." ■

Mesothelioma Drug Fails to Hold the Line

BY KERRI WACHTER
Elsevier Global Medical News

STOCKHOLM – The results of the largest clinical trial to date in malignant pleural mesothelioma have left patients still without a standard second-line treatment for this deadly tumor in the chest lining.

"Vorinostat [Zolinza] did not improve survival compared with placebo," Dr. Lee M. Krug said at the European Multidisciplinary Cancer Congress, where he reported outcomes of the disappointing phase III VANTAGE 014 trial.

Overall survival was not significantly different at a median of 31 weeks in patients on vorinostat and 27 weeks in those on placebo (hazard ratio, 0.98; $P = .858$). Planned analyses found no subgroups that had any advantage in overall survival from vorinostat use, said Dr. Krug of Memorial Sloan-Kettering Cancer Center in New York City.

The large trial 'provides an excellent source of information with regards to this patient population.'

DR. KRUG

Discussant Dr. Rolf A. Stahel of the University Hospital Zurich lamented, "This has been the largest study ever in mesothelioma. … Despite this huge effort, the result is negative."

Patients were included if they had a diagnosis of malignant pleural mesothelioma with a pleural lesion at least 1 cm in thickness. They could have received up to two prior systemic regimens with pemetrexed (Alimta) and a platinum. They had to have a Karnofsky performance status of at least 70 and adequate organ function.

Vorinostat is a histone deacetylase (HDAC) inhibitor. In all, 660 patients were randomized to vorinostat (300 mg) or placebo. Both were given orally twice daily for 3 days out of 7 days in a 3-week cycle. The population was predominantly male, with a slightly greater percentage in the vorinostat arm (86% vs. 81%). Almost all patients (90%) had stage III-IV disease.

Researchers were puzzled by a change in survival rates in patients who were measured at the time of the third interim analysis, compared with those who were enrolled after the third interim analysis, said Dr. Krug.

At the third interim analysis, the hazard ratio for overall survival was 0.86, "which was just shy of the 0.83 hazard ratio required for this to be a positive trial." After the interim analysis – which occurred halfway through the study – the hazard ratio was 1.32.

VITALS

Major Finding: Overall survival was not significantly different at a median of 31 weeks with vorinostat and 27 weeks with placebo (HR, 0.98; $P = .858$).

Data Source: A phase III trial of 660 patients with mesothelioma who were randomized to receive vorinostat or placebo as second-line therapy.

Disclosures: The study was supported by Merck Laboratories. No conflicts were reported at the meeting. Dr. Krug previously reported relationships with numerous companies, including receiving research funding from Merck.

The test of interaction between survival effect and time of enrollment, suggested that there was a less than 2% chance that this switch occurred randomly. "As yet, we have not identified any causes," Dr. Krug said.

Median progression-free survival (determined by independent radiologic review) was significantly improved statistically in the vorinostat arm but not in a clinically significant way: 6.3 weeks for vorinostat vs. 6.1 weeks for placebo (HR, 0.75; P less than .001).

Secondary end points (overall objective response rate, the dyspnea score on the Lung Cancer Symptom Scale as modified for mesothelioma, and forced vital capacity) were no better with vorinostat than with placebo. There were two confirmed radiologic responses, one in each arm.

'Despite this huge effort, the result is negative.'

DR. STAHEL

"The adverse events were comparable between the two arms. … Serious adverse events were slightly increased for some toxicities that you might expect to see with vorinostat," said Dr. Krug. These included fatigue, nausea, and dehydration. Tumor pain was greater in the placebo arm.

Despite the negative results, just by its sheer size the trial "provides an excellent source of information with regards to this patient population, such as data on their pulmonary function, [symptomatology], serum markers, and also the large tumor bank that was collected," Dr. Krug told attendees at the joint congress of the European Cancer Organization (ECCO), the European Society for Medical Oncology (ESMO), and the European Society for Radiotherapy and Oncology (ESTRO). ■

Oral Bacteria Changes May Presage Pneumonia

BY NEIL OSTERWEIL
Elsevier Global Medical News

BOSTON – In addition to causing cavities, oral microbes may be linked to the risk for health care–associated pneumonia, a small study presented at the annual meeting of the Infectious Diseases Society of America showed.

In the study, intubated patients in an ICU were found to have oral microbial profiles that were significantly different from those of similar patients who did not develop pneumonia, reported Dr. Samit Joshi of the section of infectious diseases at Yale University, New Haven, Conn.

The study investigators also found that mouth-dwelling microbe profiles of community-dwelling healthy adults differed markedly from those of adults at higher risk for pneumonia, including nursing home residents and patients on mechanical ventilation.

"We showed that as the risk for pneumonia increased among these three groups of adults, that certain types of bacteria living in their mouths decreased. Interestingly, in the adults who actually developed pneumonia, other disease-causing bacteria in their mouths actually increased days before those adults developed pneumonia," Dr. Joshi said in a briefing.

THIS DISCOVERY MAY LEAD TO NEW WAYS TO PREVENT PNEUMONIA BY MAINTAINING THE COMPOSITION OF BACTERIA THAT LIVE INSIDE OUR MOUTHS.

The findings suggest that genetic sequencing of oral microbial communities in patients' mouths may provide novel methods for targeted prevention of pneumonia, he added.

The investigators took swab samples from the mouths of 19 healthy, community-dwelling adults (mean age, 60.1 years), 10 nursing home residents (86.2 years), and 8 patients in an ICU (51.6 years). The nursing home residents had been living in the facility for a mean of 33.2 months; the ICU patients had been in the unit for a mean of 3.6 days.

Samples of bacteria collected from the palate, buccal mucosa, tongue, and gingival crevice were then analyzed with165 ribosomal RNA pyrosequencing, a sophisticated technology suitable for complex microbiome analyses but not available for bedside or point of care assays.

The authors found that bacteria in the family Streptococcaceae were the dominant oral residents, but in proportions that differed significantly among the three patient groups: 65% among community dwellers, 43% among nursing home residents, and 33% among the ICU patients, all of whom were on mechanical ventilation.

Three of the patients went on to develop pneumonia at around 1 week of their ICU stay, and these patients had significantly smaller average proportions of oral Steptococcaceae species than did ICU patients who did not develop pneumonia (0.07% vs. 49%).

The authors then looked at the mean weighted UniFrac distance, which allows for phylogenetic comparisons of microbial communities, and found a significant difference between ICU residents who developed pneumonia and those who didn't.

"This discovery has implications for how we prevent pneumonia in the future," Dr. Joshi said at the meeting. "It may lead to new and improved ways that we can prevent pneumonia by maintaining the composition of bacteria that live inside our mouths, or by maintaining our local immune defense mechanisms."

The idea that microbial communities may be markers of disease is "exciting," said Dr. David Relman, professor of medicine at Stanford (Calif.) University. "What we don't know right now is whether the two are linked causally – these changes in the microbial composition and the onset of disease – but regardless, I think there is value in understanding these novel kinds of markers of pneumococcal disease," he commented. Dr. Relman was not involved in the study, but moderated a briefing where the data were presented.

The study was funded by the National Institute on Aging and the Howard Hughes Medical Institute. Dr. Joshi and Dr. Relman each reported that they had no relevant financial disclosures. ■

Dental Plaque May Up Risk of CAP Hospitalization

VITALS

Major Finding: Community-dwelling older adults with a mean oral plaque score equal to or greater than 1 were 43% more likely to develop pneumonia that required hospitalization.

Data Source: A prospective cohort study in 1,575 adults aged 70 years and old.

Disclosures: The study was supported by grants from the National Institutes for Health. Dr. Juthani-Mehta reported that she had no relevant financial disclosures.

BY NEIL OSTERWEIL
Elsevier Global Medical News

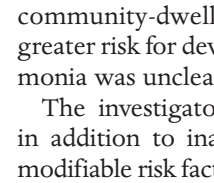
BOSTON – Community-dwelling seniors who brush their teeth, keep as active as their infirmities permit, and shun cigarettes may be able to significantly lower their risk for serious pneumonia, investigators reported at the annual meeting of the Infectious Diseases Society of America.

Among 1,575 adults aged 70 years and older who were followed in an ongoing prospective study, a higher oral plaque burden was associated with a 1.43-fold greater risk for pneumonia that required hospitalization; the development of a mobility limitation was linked to 1.84-fold increased risk, and an active smoking status effectively doubled the risk (1.95-fold), reported Dr. Manisha Juthani-Mehta of Yale University, New Haven, Conn.

"The novel and interesting thing from this study is that these findings are consistent with the emerging theme linking oral bacteria – and therefore, potentially, the oral microbiome – to pneumonia risk in many different clinical settings, not only hospital-acquired pneumonia and ventilator-associated pneumonia, but now potentially … community-acquired pneumonia, where aspiration may be a predominant mechanism for risk of pneumonia in community-dwelling older adults as well," she said.

Dental plaque has been identified as a reservoir for respiratory pathogens implicated in hospital-acquired and ventilator-associated pneumonia, and her group has identified inadequate oral care as a risk factor for nursing home–acquired pneumonia, Dr. Juthani-Mehta said.

Whether dental plaque or poor oral hygiene also puts presumably healthy, community-dwelling older adults at greater risk for developing serious pneumonia was unclear, however.



'These findings are consistent with the emerging theme linking oral bacteria … to pneumonia risk.'

DR. JUTHANI-MEHTA

The investigators hypothesized that in addition to inadequate dental care, modifiable risk factors for pneumonia include lack of influenza and pneumococcal vaccinations, poor nutrition (body mass index loss), and cigarette smoking.

The overall Health ABC study cohort included 3,075 community-dwelling adults in Pittsburgh and Memphis who were aged 70-79 years at baseline. Of that group, 1,575 had a study interview within 6 months of a dental exam and had an available plaque score.

The authors defined poor oral hygiene as a mean oral plaque score of 1 or greater on a scale of 0-3 (0 = no plaque; 1 = plaque identified by a probe; 2 = visible plaque; 3 = abundant plaque).

The rate of pneumonia cases requiring hospitalization (the primary outcome) was 169.8 per 10,000 person-years, similar to that of the overall population rate for people aged 65 years and older (161.0 per 10,000 person-years in 2007, according to a 2010 National Health Statistics Report).

In a multivariate analysis, modifiable risk factors were mean oral plaque score (hazard ratio, 1.43), incident mobility limitation (HR, 1.84), and active smoking (HR, 1.95).

Nonmodifiable risk factors included male sex (HR, 2.08), white race (HR, 1.67), and age older than 75 years (HR, 1.32).

Looking at the average attributable fraction for each of the risk factors, the investigators found that the plaque score accounted for 13.1% of pneumonias, mobility limitation accounted for 12.2%, and smoking for 1.1%. ■

Pneumonia Stay Shortened by Tapering Antibiotic

In-hospital mortality was significantly lower in the de-escalation group at 17% vs. 41% in controls.

BY DIANA MAHONEY
Elsevier Global Medical News

CHICAGO – Antibiotic de-escalation in patients with nosocomial pneumonia in the intensive care unit produced the same clinical outcome – or better – as maintaining broad-spectrum coverage through the treatment course, a study has shown.

Modifying empiric therapy by continuing with narrower-spectrum antibiotics based on culture and antibiotic susceptibility reports not only limits the emergence of multidrug-resistant pathogens, but also reduces resource utilization for the treatment of hospital-acquired pneumonia, ventilator-assisted pneumonia, and health care–associated pneumonia, Chris Destache, Pharm.D., said at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy.

The Infectious Diseases Society of America and the American Thoracic Society both advocate early broad-spectrum empiric antibiotics with subsequent streamlining based on the organisms identified by culture and the known susceptibility patterns in nosocomial pneumonia, but the effect of antibiotic de-escalation on resource utilization – particularly hospital length of stay and cost of hospitalization – has not been examined, Dr. Destache said.

To evaluate the impact of antibiotic de-escalation in the intensive care unit on these resource utilization factors, Dr. Destache of Creighton University in Omaha, Neb., and his colleagues retrospectively studied the charts of patients older than 18 years admitted to the Creighton University Medical Center ICU in 2009 with a presumptive diagnosis of hospital-acquired pneumonia (HAP), ventilator-assisted pneumonia (VAP), or health care–associated pneumonia (HCAP), who also had blood or respiratory cultures collected prior to the initiation of antibiotic treatment.

Antibiotic de-escalation was defined as the discontinuation of at least one empiric agent or the change to a narrower-spectrum antibiotic, he said.

Patients who received systemic antibacterial, antifungal, or antiviral treatment within 72 hours of their pneumonia diagnosis were excluded from the analysis.

The primary study end point was ICU length of stay; secondary end points included total hospital length of stay, in-hospital mortality, and hospitalization costs.

Of 378 records identified, 95 patients representing 99 cases of nosocomial pneumonia met the study's eligibility requirements.

"All of the patients had presumptive pneumonia based on [Centers for Disease Control and Prevention] criteria and received broad-spectrum antibiotic therapy based on universal guidelines, and de-escalation was performed in 60 cases," Dr. Destache reported. Universal guidelines call for patients to receive piperacillin-tazobactam, levofloxacin, and vancomycin for at least 24 hours.

Patients in whom the streamlined antibiotic approach was utilized were more likely to be older than those in whom empiric treatment was maintained, with a mean age of 66 years compared with 55.5 years, he said, noting that patients in the de-escalation group were also more likely to have diabetes (38% vs. 18%) and to have cardiovascular disease (38% vs. 15%).

No differences in sequential organ failure assessment scores were observed between the two groups at baseline, although these scores at culture finalization were significantly lower in the de-escalation group, which may have been a factor in the decision to de-escalate, Dr. Destache said.

The ICU length of stay was shorter in the de-escalation group at 9.4 days, compared with 12.8 days in the empiric treatment group, although the difference was not significant.

Total length of stay was also shorter, at 15.3 vs. 16.9 days, and hospitalization costs were lower, at $45,640 vs. $60,640, Dr. Destache said at the meeting, which was sponsored by the American Society for Microbiology.

In-hospital mortality was significantly lower in the de-escalation group at 17%, compared with 41% in controls.

Culture was negative in 39 of the de-escalation cases and 18 of the controls, and was positive in 21 of each group, Dr. Destache said.

THE FINDINGS CONFIRM THE FEASIBILITY AND CLINICAL BENEFIT OF ANTIMICROBIAL DE-ESCALATION IN NOSOCOMIAL PNEUMONIA.

The most common causative pathogens identified in the de-escalation group were methicillin-resistant *Staphylococcus aureus* (MRSA), followed by methicillin-susceptible *S. aureus* (MSSA), *Pseudomonas aeruginosa*, and *Streptococcus pneumoniae*, he said. In the control group, the most common was MSSA, followed by *P. aeruginosa* and *S. pneumoniae*, he said.

In comparing the benefits of antibiotic de-escalation based on culture status, the investigators found that "culture-negative pneumonias derived the greatest benefit from de-escalation," Dr. Destache said.

In culture-negative pneumonias, the de-escalation group had an ICU stay of 7.2 days, a total length of stay of 10.4 days, and a mortality of 10%; in the culture-negative control group, ICU stay was 11.9 days, total length of stay was 15.1 days, and mortality was 50%, he said.

Culture-positive patients in the de-escalation group stayed in the ICU for 13.6 days and in the hospital for 24.5 days, both lengths of time that were statistically similar to the 13.6 days and 18.5 days in the control group.

The overall mortality rates were 29% in the de-escalation group and 33% in the standard treatment group.

The findings confirm the feasibility and clinical benefit of antimicrobial de-escalation in nosocomial pneumonia and indicate that the strategy reduces resource utilization, compared with maintaining broad-spectrum coverage, Dr. Destache said.

As such, he added, the treatment strategy should be utilized when appropriate as a way to improve antimicrobial stewardship, he noted. ■

VITALS

Major Finding: The ICU length of stay for patients with nosocomial pneumonia in whom initial empiric antibiotic therapy was de-escalated was 9.4 days, compared with 12.8 days in patients maintained on empiric therapy.

Data Source: A retrospective chart study comparing the impact of antibiotic de-escalation relative to maintenance on broad-spectrum therapy on resource utilization in 99 cases of nosocomial pneumonia.

Disclosures: Dr. Destache said he had no relevant financial disclosures.

COMMENTARY

Dr. Marcos Restrepo, FCCP, comments: This is a very interesting study, emphasizing the importance of de-escalation in order to prevent antimicrobial resistance and overuse of unnecessary antibiotics. The expectations that this approach would improve clinical outcomes will be a motivation for larger prospective studies using antimicrobial stewardship strategies.

Pages 16a—16b

Ultrasound Assessment in Pneumonia Cut Surgeries

Readmission rates dropped significantly from 8% before the algorithm to none after.

BY MITCHEL L. ZOLER
Elsevier Global Medical News

BOSTON – A hospital-wide algorithm for diagnosing and managing complicated bacterial pneumonia in children led to a marked cut in unnecessary chest CT examinations and a reduced number of surgical interventions. It also produced better outcomes, with fewer readmissions and no change in average length of stay or vancomycin use.

'Some patients didn't need VATS, and so the algorithm reduced unnecessary interventions.'

DR. DEBIASI

A key element of the management algorithm, implemented 3 years ago for children with a pleural effusion, empyema, or both complicating community-acquired bacterial pneumonia, was the emphasis on assessing children with ultrasound rather than with CT. This change produced a drop in chest CT examinations in these patients from 60% before the algorithm became hospital policy to 17% after.

The algorithm called for preferentially using ultrasound to assess these cases. During the first 15 months of its use, chest ultrasound in these patients was performed in 71% of cases, compared with 27% of cases before the algorithm, Dr. Roberta L. DeBiasi said at the annual meeting of the Infectious Diseases Society of America.

The preferential use of more ultrasound examinations in children with a pleural-space infection meant that fewer children received the large radiation dose delivered by a CT exam and the sedation required for CT.

While safer, ultrasound also produces better imaging than CT in these patients "to sort out who has a loculated empyema that needs VATS [video-assisted thoracic surgery] and who has a nonloculated effusion that generally doesn't need VATS," said Dr. DeBiasi, a pediatric infectious diseases specialist on the staff of Children's National Medical Center in Washington.

Creation of a new algorithm for the hospital depended on getting physicians and surgeons from all the divisions and departments involved in managing these children – infectious diseases, surgery, radiology, hospitalists, pulmonology, and emergency department – together to decide on the best management approach and make it hospital policy.

"We asked, don't you realize there are data that ultrasound is preferable, so why use CT so often? The answer was that an ultrasound technician wasn't available at night in the emergency room," she said.

After seeing the data, the radiologists agreed that having ultrasound available 24/7 was important and took the steps needed to arrange it, Dr. DeBiasi said in an interview. The hospital gets on average one or two patients a week with community-acquired bacterial pneumonia complicated by a pleural space infection.

Although no society guidelines existed in November 2008 when the revised algorithm went into effect, last August the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America issued joint recommendations on the management of community-acquired pneumonia in children and included a recommended approach similar to the Children's National algorithm, Dr. DeBiasi said (Clin. Infect. Dis. 2011 Aug. 30 [doi: 10.1093/cid/cir531]).

The only difference was that her hospital's guidelines are more specific, and guide the staff through the local protocol step by step.

For example, the new society recommendations say that either video-assisted thoracic surgery or fibrinolytic therapy are appropriate options for managing loculated empyema. Because surgeons at Children's National Medical Center do not use fibrinolytic therapy on these cases, the algorithm specifies VATS only, she said.

To examine the impact of the algorithm, Dr. DeBiasi and her associates analyzed patient management and outcomes during the 15 months before the revised algorithm went into effect and then during the first 15-month period after.

The review showed that the 83 patients managed before November 2008 were an average of 6 years old, similar to the 87 patients treated during the first 15 months using the algorithm, who were an average of 5 years old.

The reduced number of CT exams and increased ultrasound use led to a reduction of VATS from 45% of cases before the algorithm to 29% after.

Patient outcomes were better – with a "nice" statistically significant drop in readmission rates from 8% before the algorithm to none during the period after it took effect.

However, during both periods, vancomycin use and average length of stay remained constant (35% and 8 days, respectively), Dr. DeBiasi noted.

"Our [inference] is that some patients didn't need VATS, and so the algorithm reduced unnecessary interventions. These patients were just managed medically," Dr. DeBiasi said. "I think it was the ultrasound that led to less VATS, because ultrasound is better than CT to see who needs VATS and who doesn't." ■

VITALS

Major Finding: A hospital algorithm for management of children with complicated bacterial pneumonia that called for ultrasound to assess the pleural space led to a drop in surgical procedures from 45% to 29%; readmissions were reduced from 8% to none.

Data Source: Retrospective review of 83 patients treated for complicated bacterial pneumonia before institution of a revised management algorithm and 87 patients after the revised protocol was in place at a single U.S. medical center.

Disclosures: Dr. DeBiasi said that she did not have any disclosures.

Factors May Predict Cardiac Events in CAP Inpatients

BY SUSAN LONDON
Elsevier Global Medical News

Certain hospitalized adult patients with community-acquired pneumonia may require closer monitoring and perhaps intervention because they are at increased risk for acute cardiac events, research suggests.

In a prospective cohort study of 3,921 such patients, 8% had an acute cardiac event, investigators found. A history of heart disease, hypoalbuminemia, older age, and several other factors conferred an increase in the odds of such events, and a prediction score incorporating these factors had an area under the receiver operating characteristic curve of 0.74.

It may be possible to apply this new information to improve patient outcomes, according to Dr. Carolina Garcia-Vidal, of Bellvitge University Hospital in Barcelona, who presented her research team's data at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy.

"The first thing is you have to recognize which patients are at high risk. And then in that population, maybe you have to do some extra things," she explained in an interview. "Maybe you have to follow [the patient] closer, maybe you have to follow in a special way, such as with a cardiac monitor."

Increased cardiac stress, hypoxemia, and inflammation may all contribute to cardiac events in patients with CAP, Dr. Garcia-Vidal noted. Regarding the last, "if you are able to relate these events with a proinflammatory effect, maybe you can do something to modulate this inflammatory [state]. I think that's the future."

The investigators prospectively studied 3,921 adult inpatients treated in the hospital between 1995 and 2010 who had CAP and did not have severe immunosuppression.

Overall, 8% of the patients experienced at least one acute cardiac event (myocardial infarction, new or worsening arrhythmia, and/or new or worsening congestive heart failure) during their hospital stay, according to results reported in a poster session at the conference, which was sponsored by the American Society for Microbiology.

"These patients have a mortality that is very high," Dr. Garcia-Vidal pointed out. In fact, they were about three times more likely to die within 30 days than their event-free counterparts (19% vs. 6%).

In a multivariate analysis, patients had significantly higher odds of acute cardiac events if they were older than 65 years or had heart disease, kidney disease, tachycardia, hypotension, hypoalbuminemia, multilobar pneumonia, or pneumococcal pneumonia, with odds ratios ranging from 1.37 to 3.03.

The factors were combined to create a 9-point score, which had an area under the receiver operating characteristic curve of 0.74 for predicting acute cardiac events. The rate of such events was 19% among patients falling into a high-risk group, defined as having a score of 3 or higher.

The investigators plan to validate the model in another patient population, according to Dr. Garcia-Vidal. ■

VITALS

Major Finding: Eight factors independently predicted acute cardiac events (odds ratios, 1.37-3.03). When they were combined into a prediction score, the area under the receiver operating characteristic curve was 0.74.

Data Source: A prospective cohort study among 3,921 hospitalized adults with community-acquired pneumonia.

Disclosures: The researchers reported having no relevant conflicts of interest.

COMMENTARY

Dr. Jun Chiong, FCCP, comments: The study investigators reaffirm the fact that pneumonia in patients with several risk factors puts them at a higher risk for acute cardiac events in the hospital. It's important to note that this patient population should be monitored closely and the threshold of testing for acute coronary syndrome is lowered, especially when the symptom of chest pain arises or if dyspnea from pneumonia persists after optimal therapy.

Moxifloxacin Noninferior for COPD Exacerbations

BY SUSAN LONDON
Elsevier Global Medical News

CHICAGO – Moxifloxacin works as well as the combination of amoxicillin and clavulanic acid in the treatment of acute exacerbations of complicated chronic obstructive pulmonary disease, new data show. But the former may have the edge in cases in which a bacterial pathogen is identified.

In a randomized, double-blind, noninferiority trial among 1,352 patients who had complicated COPD and an exacerbation, about a fifth of patients had a clinical failure of their antibiotic therapy, no matter which regimen they received, according to results reported at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy.

However, secondary analyses showed that in the subset of patients in whom a bacterial pathogen was identified in sputum before antibiotic therapy was started, clinical failure was significantly less likely for those who received moxifloxacin, which is a member of the fluoroquinolone class of antibiotics.

"I think, clinically, what this translates to is, yes, you can use either antibiotic in this group," lead investigator Dr. Sanjay Sethi said in an interview at the conference, which was sponsored by the American Society for Microbiology. But in patients in whom a bacterial pathogen is identified or strongly suspected, "moxifloxacin does better in that subgroup."

VITALS

Major Finding: The rate of clinical failure within 8 weeks of the end of therapy was noninferior with moxifloxacin vs. amoxicillin–clavulanic acid in both the per-protocol population (20.6% vs. 22.0%) and the intent-to-treat population (20.4% vs. 21.6%).

Data Source: A randomized, double-blind, noninferiority trial among 1,352 patients with complicated COPD who had an acute exacerbation (the MAESTRAL trial).

Disclosures: Dr. Sethi reported that he is an investigator for and scientific adviser to Bayer HealthCare Pharmaceuticals and has received speaker honoraria and consulting fees from the company. The trial was supported by Bayer HealthCare Pharmaceuticals.

The difference seems to be driven by better bacterial eradication with moxifloxacin, he added. "So when you have a well-defined pathogen, you eradicate the bacterium [and] you get a clinical difference in outcomes."

Both antibiotics were well tolerated, according to Dr. Sethi. Moxifloxacin may have a slight advantage in terms of convenience, as it was given once daily for 5 days, compared with twice daily for 7 days for the amoxicillin–clavulanic acid. Comparative costs will depend on the local market and availability of generic formulations.

Some guidelines, such as the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, list the two antibiotic regimens as equal alternatives for patients with complicated COPD, such as those having underlying severe airflow obstruction, recurrent exacerbations, or comorbid cardiac disease, according to Dr. Sethi, chief of the division of pulmonary, critical care, and sleep medicine at the State University of New York at Buffalo.

"What this study tells me is, I think that we did that right," that is, listing the two regimens as alternatives, he commented. "These are secondary analyses, but there could be a subgroup with a predominant pathogen [in whom] there may be differences between the two."

In a novel finding, the study also showed that early bacterial eradication at the end of antibiotic therapy increased the likelihood of clinical cure at 8 weeks later, no matter which antibiotic the patients received. This association "has not been very well described in COPD exacerbations," Dr. Sethi noted.

Patients with COPD were eligible for the trial, called MAESTRAL (Moxifloxacin vs. Amoxicillin–Clavulanic Acid in Treatment of Acute Exacerbation of Chronic Bronchitis), if they were aged 60 years or older, had an Anthonisen type 1 exacerbation (with purulent sputum, increased sputum volume, and increased dyspnea), had a forced expiratory volume in 1 second (FEV_1) of less than or equal to 60% of predicted, and had experienced more than two exacerbations in the last year that required systemic antibiotics and/or systemic corticosteroids.

The subjects were randomized in equal numbers to receive moxifloxacin (400 mg orally once daily for 5 days) or amoxicillin plus clavulanic acid (875 and 125 mg orally twice daily for 7 days). Sputum samples were collected before start of therapy and serially thereafter for Gram staining and culture.

The trial's primary end point was the rate of clinical failure (defined as the need for additional or alternative treatment for the exacerbation with systemic antibiotics, systemic corticosteroids, and/or hospitalization) within 8 weeks of the end of antibiotic therapy. The investigators defined noninferiority as a difference in the rate of this end point of no more than 6% between groups.

The patients studied were 70 years old on average, and 80% were men. Slightly more than a third used systemic corticosteroids. Their mean FEV_1 was about 980 mL, and their mean number of exacerbations in the previous year had been 2.5.

Study results, reported in a poster session, showed that the rate of clinical failure was noninferior with moxifloxacin, compared with amoxicillin–clavulanic acid, in both the intent-to-treat population (20.4% vs. 21.6%) and the per-protocol population (20.6% vs. 22.0%).

Slightly fewer than half of patients had at least one potentially pathogenic bacterium isolated from sputum before starting antibiotic therapy, most often *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Staphylococcus aureus*.

In this subset of patients, the rate of clinical failure was lower with moxifloxacin than with amoxicillin–clavulanic acid in both the intent-to-treat population (19.0% vs. 25.4%; $P = .02$) and the per-protocol population (19.2% vs. 26.1%; $P = .03$). Further analysis showed higher rates of bacterial eradication with moxifloxacin, mainly driven by higher rates of eradication of *H. influenzae* (89.2% vs. 66.7%).

In the study population overall, patients who had bacteriologic eradication at the end of antibiotic therapy, compared with bacteriologic persistence or superinfection, were more likely to be cured 8 weeks later (79.7% vs. 54.7%, *P* less than .001). The finding was the same in the two treatment groups individually.

The rate of drug-related adverse events was 7.8% with moxifloxacin and 6.1% with amoxicillin–clavulanic acid. The most common events were headache, diarrhea, and fever. ■

COMMENTARY

Dr. Darcy Marciniuk, FCCP, comments: Trials powered to demonstrate noninferiority remind me of coming in second place – you feel good but wonder if you could have done better if you had tried harder. Nonetheless, in this population of patients with moderate or severe COPD and a past history of frequent exacerbations, both oral moxifloxacin and amoxicillin-clavulanic acid proved effective. Although secondary analysis demonstrated superiority in subjects in whom a bacterial pathogen was identified, this result is less practical when choosing empiric therapy for the patient who has an acute exacerbation of COPD. An important finding, however, was that early bacterial eradication increased the likelihood of clinical cure 8 weeks later. This highlights the value of effective targeted antimicrobial therapy in this setting.

Influenza Vaccine Coverage Far From Perfect

BY MIRIAM E. TUCKER
Elsevier Global Medical News

There are substantial gaps in the evidence supporting the effectiveness of influenza vaccines, particularly in the elderly, according to the findings of large systematic review and meta-analysis published online Oct. 25 in the Lancet Infectious Diseases.

Although the published report highlights the dearth of strong and consistent efficacy and effectiveness data for influenza vaccine in studies that met very strict criteria, it should not be interpreted as a suggestion to stop vaccinating, according Michael T. Osterholm, Ph.D., the study's lead author and director of the center for infectious disease research and policy at the University of Minnesota, Minneapolis.

Dr. Osterholm said his intent in conducting and publishing this analysis was not to cast doubt on current influenza immunization efforts, but rather to influence the pace of new vaccine development.

"There is a major barrier to entry right now for venture capital and start-up companies to bring new novel technologies forward. When you have a vaccine that's universally recommended, said by public health to be effective, and is quite cheap, why would anybody spend a billion dollars to try to make a new vaccine?"

Of a total 5,707 studies published from 1967 through Feb. 15, 2011, just 31 (17 randomized and 14 observational studies) met a list of strict criteria, the most salient being the use of influenza confirmed by culture or real-time polymerase chain reaction as an outcome (Lancet Infect. Dis. 2011 Oct. 25 [doi:10.1016/S1473-3099(11)70295-X]).

The analysis included studies of both the trivalent inactivated vaccine (TIV) and the live attenuated (intranasal) influenza vaccine (LAIV). Among the 10 randomized, controlled trials of TIV over 12 influenza seasons, analyses for 8 of the seasons showed significant efficacy, whereas 4 did not. Of eight studies that were conducted in healthy adults aged 18-64 years over a total of nine flu seasons, the pooled efficacy was 59%. One study conducted in children aged 6-24 months over two flu seasons produced dramatically different efficacy results: 66% in the first year, –7% in the next (JAMA 2003;290:1608-16). The "minus" essentially means zero, rather than suggesting an increased risk from the vaccine, Dr. Osterholm said in the interview.

No randomized, controlled trials met the criteria for children aged 2-17 years, or for adults aged 65 years and older. Indeed, conducting placebo-controlled trials in adults aged 65 and older would be considered unethical because influenza vaccine has been recommended for that age group since 1960, the authors noted.

The picture for LAIV was different: Of the 10 randomized controlled trials assessing LAIV efficacy during 12 flu seasons, 9 showed significant efficacy. All of these were done in healthy individuals. In children aged 6 months to 7 years, there were six studies covering eight influenza seasons. The vaccine was effective in all eight, with a pooled efficacy of 83%.

But LAIV data in other age groups were less impressive. One study of LAIV in adults aged 60 and older showed significant overall efficacy (42%), but – oddly – efficacy was lower in those aged 60-69 years and higher in those aged 70 and older (Vaccine 2009;28:228-34).

Of three randomized, controlled trials of LAIV in adults aged 18-49, none showed significant protection, Dr. Osterholm and his associates reported.

Vaccine effectiveness varied in the nine observational trials of seasonal flu vaccine, with 6 of 17 embedded analyses showing significant protection against medically attended, laboratory-confirmed influenza. Of the five observational studies that assessed effectiveness of the 2009 pandemic H1N1 vaccine, median efficacy was 69% (range, 60%-93%).

Except for the LAIV studies in children aged 7 years or younger, the data showed substantial variability by influenza season and by age group. In some influenza seasons, the level of protection was low or not evident. In contrast to the 70%-90% overall effectiveness that is often cited for the vaccine in seasons when the vaccine is well matched to circulating strains, "we noted this magnitude of effectiveness only for LAIV use in children aged 7 or younger," Dr. Osterholm and his associates wrote.

"The bottom line is we have to recognize we need these vaccines and we need them now. If this paper does anything, it's a clarion call that we need to really fast-forward our novel influenza vaccine program forward, and quickly," Dr. Osterholm said. "But in the meantime, we should maintain public support for the present vaccines that are the best intervention available for seasonal influenza."

The analysis, funded by the Alfred P. Sloan Foundation, is part of a much larger CIDRAP report on influenza vaccine that is due out later this year.

Dr. Osterholm stated that neither he nor his coauthors have any financial disclosures. ■

EGFR Assay Vastly Underused in Lung Cancer

BY ALICIA AULT
Elsevier Global Medical News

WASHINGTON – An assay that can detect the presence of epidermal growth factor receptor mutations in non–small cell lung cancer patients is being vastly underused in the United States, according to a study presented at the conference sponsored by the American Association of Cancer Research.

An EGFR diagnostic was launched by Genzyme Corp. in 2005. Patients with EGFR mutations generally respond better to certain therapies – such as erlotinib (Tarceva) and geftinib (Iressa) – that target these mutations.

Earlier this year, the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) recommended EGFR testing for lung cancer patients. ASCO's provisional clinical opinion advocated that patients with advanced NSCLC who were being considered for treatment with a tyrosine kinase inhibitor should be tested for EGFR mutations. The NCCN called for EGFR testing after histologic diagnosis of adenocarcinoma, large cell carcinoma, or undifferentiated carcinoma, but not in patients with squamous cell disease, which is less likely to be EGFR positive.

THE COUNTIES WITH THE HIGHEST LUNG CANCER INCIDENCE HAVE THE LOWEST RATE OF EGFR TESTING.

And yet, it appears that the assay is not being widely used, said Julie Lynch, R.N., a research assistant at the University of Massachusetts, Boston, who conducted the study.

After conducting a systematic review of erlotinib trials, Ms. Lynch, a PhD nursing candidate, was concerned that few blacks or Hispanics were enrolled. She decided to determine whether minorities might not be included because they were not being tested for the EGFR mutations.

Genzyme agreed to share the data it had with Ms. Lynch. The Genzyme database represents an estimated 98% of community hospital use of the EGFR assay. However, it does not present a comprehensive picture. Ms. Lynch had very little data from the 59 cancer centers with special designation from the National Cancer Institute. Many of these NCI centers have separate licenses from Genzyme or conduct their own assays for research purposes.

To get a better picture of where these tests were being used, she merged Genzyme's data on EGFR testing with public data sets from the U.S. Census Bureau, the Centers for Disease Control and Prevention, the National Institute of Standards and Technology, the Centers for Medicare and Medicaid Services, and the NCI. She linked test orders to specific providers to create a nationwide map that shows county-by-county use of EGFR testing.

Ms. Lynch found that in 2010, some 6,056 tests were ordered by acute care hospitals, 93 by federal hospitals (primarily Veterans Affairs hospitals), 527 by pathology labs, and 258 by independent outpatient oncology clinics or physicians. She was able to ascertain that some 1,019 EGFR tests were ordered by NCI centers, but again, this is likely only a partial tally.

To put these numbers in perspective, the American Cancer Society estimates that there will be 221,130 new cases diagnosed in 2011 for all types of lung cancer combined. Non–small cell lung cancers account for 80%-90% of all lung cancers.

Test orders seemed to be clustered around NCI-designated centers, Ms. Lynch said in an interview. Most likely, community hospitals within a relatively close distance to those NCI centers ordered more EGFR tests to compete.

Her data showed huge regional variations in EGFR testing. The test was ordered in only 357 of the 3,142 counties in the United States. The largest concentrations were in Nassau County, N.Y.; New York County, N.Y.; Baltimore County, Md.; Kent County, Mich.; and Cook County, Ill. Also in the top 10 were Brooklyn, N.Y., and the counties surrounding Phoenix, Boston, Miami, and Los Angeles. Most of those top users were very close to an NCI-designated center.

VITALS

Major Finding: Only about 8,000 orders for EGFR assays could be verified in 2010.

Data Source: A nationwide map based on a Genzyme company database and public data sets.

Disclosures: The study was funded by grants from the U.S. Department of Education and the National Institutes of Health, and was aided by the provision of data by Genzyme Genetics. Ms. Lynch is a former employee of Genentech.

When Ms. Lynch excluded the tests ordered by NCI centers, she found a bleak picture: Not a single test was ordered in Alaska; there is no NCI-designated center in that state. One test was ordered in Montana, one in Vermont, and two in Wyoming; there are no NCI centers in those states. Only five tests were ordered in Utah, despite the presence of the Huntsman Cancer Institute at the University of Utah in Salt Lake City.

Only six tests were ordered in Arkansas and six in New Mexico.

The top states for EGFR testing were New York (1,024), Florida (496), California (352), Pennsylvania (338), Massachusetts (334), Maryland (284), and Illinois (272 tests).

She found that the counties with the highest lung cancer incidence have the lowest rate of EGFR testing. It's also apparent that minorities and people with a lower socioeconomic and educational status, or those who live in rural areas, are not getting access to the EGFR test, said Ms. Lynch.

She is currently accumulating Medicare-specific data for EGFR testing, which, along with the Genzyme data, should give a complete picture. The federal health program began reimbursing EGFR testing in 2009.

Ms. Lynch ruled out reimbursement issues and technological constraints as factors in underuse of the tests, but acknowledged that even with Medicare coverage, it could be an expensive proposition for a beneficiary, as they have a 20% copay. The test costs $600-$800, she said.

EGFR testing needs to be more widespread, said Ms. Lynch, noting that not only does it help patients get the best treatment, but that it also provides crucial data for the development of new therapies. ■

CT Screens for Lung Cancer Also Can Detect COPD

BY MARY ANN MOON
Elsevier Global Medical News

Unenhanced low-dose CT scans that are used to screen heavy smokers for lung cancer also can identify a substantial percentage of cases of early-stage chronic obstructive pulmonary disease, according to a report in the Oct. 26 issue of JAMA.

The results must still be validated in other cohorts, but "if CT scanning becomes widely adopted for lung cancer screening," it also could be used as a secondary test, outside of the primary and preferred method of screening with pulmonary function testing, to detect COPD early, wrote Dr. Onno M. Mets of the department of radiology at University Medical Center Utrecht (the Netherlands) and his associates.

"Early diagnosis is important because smoking cessation early in the COPD disease process slows disease progression and decreases morbidity and mortality," the authors noted.

Current CT technology "allows rapid in vivo evaluation of emphysematous parenchymal destruction and small airways dysfunction" by the assessment of air trapping, which "allows information on COPD-related changes to be obtained from CT studies performed for other reasons, such as lung cancer screening.

"We hypothesized that CT-based lung cancer screening in heavy smokers could provide an opportunity to acquire information on the presence of COPD, without the need for obtaining pulmonary function testing," Dr. Mets and his associates wrote.

They assessed a subsample of 1,140 current and former smokers participating in the Dutch Belgian Randomised Lung Cancer Screening Trial who underwent inspiratory and expiratory CT scanning, as well as pulmonary function testing, as part of the protocol for that trial.

VITALS

Major Finding: Unenhanced, low-dose CT scans to screen for lung cancer had a sensitivity of 63%, a specificity of 88%, a positive predictive value of 76%, and a negative predictive value of 79% in identifying COPD.

Data Source: An ancillary study of 1,140 men who were heavy current or former smokers and underwent CT lung scans in the Dutch and Belgian Lung Cancer Screening Trial.

Disclosures: This study was supported by the Netherlands Organisation for Health Research and Development, Dutch Cancer Society Koningin Wilhelmina Fonds, Stichting Central Fund Reserves of Former Voluntary National Health Service Administration Insurances, Siemens Germany, Rotterdam Oncologic Thoracic Steering Committee, G. Ph. Verhagen Trust, Flemish League Against Cancer, Foundation Against Cancer, and the Erasmus Trust Fund. None of the authors had financial conflicts of interest.

All of the study participants were men aged 50-75 years (mean, 63). All had a smoking history of at least 16 cigarettes per day for 25 years or at least 11 cigarettes per day for 30 years – the equivalent of 16.5 pack-years.

Based on the results of pulmonary function testing, 437 men had COPD.

The CT scans accurately identified COPD in 274 of those men and gave false-positive results in 85. Thus, CT scans had a sensitivity of 63%, a specificity of 88%, a positive predictive value of 76%, and a negative predictive value of 79% in this cohort, Dr. Mets and his colleagues reported (JAMA 2011;306:1775-81).

The investigators detected COPD in 150 (54%) of 277 men with mild obstruction, 99 (73%) of 135 with moderate obstruction, and 25 of 25 with severe obstruction.

CT was more accurate in identifying COPD among men who were symptomatic than among those who were asymptomatic. This is probably because symptomatic men had more advanced disease, they said.

"Because smokers die not only from lung cancer but also from COPD and cardiovascular disease, the rationale for evaluating lung cancer screening CT scans for additional information may prove important," the investigators concluded. ■

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.

Obesity Might Be a Risk Factor for Asthma

©NOEL MOORE/FOTOLIA.COM

The relationship between BMI and airway hyperresponsiveness increased in stepwise fashion, from an odds ratio (OR) of 1.15 for obesity class 1 to an OR of 1.46 for obesity class 2 and an OR of 1.50 for obesity class 3.

BY DOUG BRUNK

Elsevier Global Medical News

HONOLULU – A large, long-term study suggests that obesity is significantly associated with airway hyperresponsiveness, and therefore it might be a risk factor for asthma.

"There is definitely a relationship between obesity and the risk of having airway hyperresponsiveness, and maybe asthma," lead investigator Dr. Manon Labrecque said during an interview in advance of the annual meeting of the American College of Chest Physicians where the study was presented during a poster session.

"But how is it mediated? What is the explanation? It seems to be related to the mechanical effect of obesity on the volume of the lungs, [but] some other analysis of the data will permit us to better understand," Dr. Labrecque said.

The investigators reviewed the medical records of 17,195 patients with a mean age of 48 years who were referred to the Hôpital du Sacré-Coeur de Montréal, for confirmation of an asthma diagnosis between 1980 and 2000.

They then analyzed the data in order to classify patients as having obesity class 1 (body mass index of 30-34.9 kg/m^2), class 2 (BMI of 35-39.9 kg/m^2), or class 3 (BMI more than 40 kg/m^2), and compared them with normal-weight patients (those with a BMI between 18.5 and 25 kg/m^2). To define airway hyperresponsiveness, the study used a standard criterion: methacholine challenge cutoff of less than 8 mg/mL for causing a 20% fall in FEV_1 (forced expiratory volume in 1 second).

Perhaps 'it's not the fat itself that is responsible for the risk of asthma, but its mechanical effect on the lung's volume.'

DR. LABRECQUE

Of the 17,195 patients, 5,623 (33%) demonstrated airway hyperresponsiveness. The relationship between BMI and airway hyperresponsiveness increased in stepwise fashion, from an odds ratio (OR) of 1.15 for obesity class 1 to an OR of 1.46 for obesity class 2 and an OR of 1.50 for obesity class 3.

"We need more analysis to see if the effect of obesity on airway hyperresponsiveness is still there when we correct for lung volume [measures] like the FEV_1," said Dr. Labrecque, a pulmonologist at the hospital who is also affiliated with the department of medicine at the University of Montreal. "If the relation between BMI and airway hyperresponsiveness disappears after this correction, that could mean that it is not the fat itself that is responsible for the risk of asthma, but its mechanical effect on the lung's volume."

In their poster, the researchers wrote that if asthma is added to the list of conditions related to obesity, "reducing the prevalence of obesity could be expected to produce even greater public health benefits than are currently estimated."

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

Asthma Blunted Worst H1N1 Outcomes

BY JENNIE SMITH

Elsevier Global Medical News

Asthma patients hospitalized during the influenza A(H1N1) pandemic had less-severe outcomes than those without asthma, U.K. researchers have found.

People with asthma saw a lower risk of dying or requiring intensive care than did nonasthmatics, including people without any comorbidities. They were just as sick as nonasthmatics at admission. And the difference in outcomes could not be wholly ascribed to asthmatics' use of inhaled steroids: Nonasthmatics taking inhaled steroids for other conditions did not see any protective effect.

A multivariate analysis showed asthma itself to be an independent factor for less-severe outcomes in patients hospitalized with H1N1.

This finding, from a prospective cohort of 1,520 people admitted to 75 different U.K. hospitals during the pandemic, was "surprising," said Dr. Malcolm Semple, the University of Liverpool, England, who presented his findings to the European Respiratory Society annual congress in Amsterdam.

However, it did align with recent results from a global analysis of 70,000 H1N1 patients, in which asthma was also seen to be associated with less severe outcomes (PLoS Med 2011;8:e1001053).

"Respiratory viruses cause exacerbations of asthma, and so it would be tempting to assume that these people were admitted with exacerbations of asthma – that they were less sick than the rest," Dr. Semple said in an interview. "But if anything, they were more sick, with more dyspnea and the same amount of radiological changes of pneumonia" as the other patients admitted to a hospital, he said.

For their research, Dr. Semple and his colleagues used data from a prospective cohort in a study funded by the U.K. Department of Health during the H1N1 pandemic of 2009 and 2010. The cohort was used to provide real-time information on the pandemic and its clinical features to the Department of Health, and data collected were standardized to include information on age, comorbidities, inhaled steroid use, time from symptom onset to admission, and medications administered in the hospital.

"It was something innovative that we had never tried before," Dr. Semple said of the cohort, adding that its large size "allowed us to catch this signal – it would be very hard to replicate this study in a nonpandemic situation."

The researchers found that the asthmatics, who composed a quarter of the cohort (n = 385), were half as likely as nonasthmatics to die or require intensive care (11.2% vs. 19.8%; unadjusted odds ratio, 0.51), despite similar rates of pneumonia at admission.

Three variables – inhaled steroid use, admission within the first 4 days of symptoms, and systemic steroid use – were all seen as contributing to less severe outcomes for asthmatics. However, even after adjusting for these, simply having asthma was still associated with a 45% reduced likelihood of death or intensive care (adjusted OR, 0.55).

Asthmatics taking inhaled steroids were significantly less likely to die or require intensive care (7.4%) than were those not taking inhaled steroids (15.4%).

But inhaled steroids protected only the asthmatics in the study. About a fifth of the patients taking inhaled steroids were not taking them for asthma – and these patients saw no benefit, meaning that the findings do not support the use of inhaled corticosteroids in nonasthmatics.

"Do steroids protect everyone? No. But do steroids protect asthmatics? Emphatically, yes," Dr. Semple said. "The implication for practice is that, if you have a diagnosis of asthma, you should adhere to the published guidance if you're a physician; and if you're a patient, you should do as you're told and take your steroids regularly."

Dr. Semple and his colleagues' study was funded by the U.K. Department of Health. The researchers disclosed no conflicts of interest. ■

COMMENTARY

Dr. Darcy Marciniuk, FCCP, comments: The results from this study are indeed surprising – who would have predicted that patients with asthma would have better outcomes during an influenza pandemic? The use of corticosteroids and prompt initiation of therapy (admission to hospital within 4 days of symptoms) were associated with less severe outcomes in the asthmatic patients. But even after adjusting for these variables, patients with asthma had a significantly reduced likelihood of death or ICU admission compared with nonasthmatic patients. As mentioned by the authors, these outcomes are yet another reason to ensure that your patients with asthma are well controlled and adherent to prescribed therapies.

ECMO Reduced Hospital Mortality in H1N1 Patients

BY HEIDI SPLETE

Elsevier Global Medical News

Hospital mortality rates were 55% lower in 2009 influenza A (H1N1) patients with severe acute respiratory distress syndrome who received extracorporeal membrane oxygenation compared with non-ECMO controls, based on data from a cohort study of 80 patients.

Data from a recent randomized trial showed that patients with acute respiratory distress syndrome (ARDS) who were transferred to an ECMO center were more likely to survive without severe disability compared with non-ECMO patients, but the role of the treatment remains controversial because of the increased costs associated with its use, said Dr. Moronke Noah of Glenfield Hospital in Leicester, England, and colleagues.

In this study, the researchers used data from the Swine Flu Triage (SwiFT) study to compare mortality rates in patients with ARDS resulting from the 2009 H1N1 flu who received ECMO with non-ECMO controls. SwiFT was a prospective study of patients with suspected or confirmed 2009 H1N1 flu who were referred for critical care. The findings were simultaneously presented at the European Society of Intensive Care Medicine and published online (JAMA 2011 Oct. 5 [doi:10.1001/jama.2011.1471]).

The researchers reviewed data from 80 patients who were referred for ECMO. They used three different matching techniques: individual matching, propensity scoring, and GenMatch matching. A total of 59 patients were matched with non-ECMO controls using individual matching, 75 were matched with non-ECMO controls using propensity scoring, and 75 were matched with non-ECMO controls using GenMatch matching. GenMatch "combines propensity score matching with multivariate matching," the authors explained.

The hospital mortality rates were significantly lower among ECMO patients than among non-ECMO patients in each of the three matching techniques. Hospital mortality rates were 24% in ECMO patients and 53% in non-ECMO patients when individual matching was used; 24% and 47% when propensity scoring was used; and 24% and 51% with GenMatch.

The findings were limited by the possible role of unobserved confounding variables, and by the lack of data on the exact treatment protocols of non-ECMO patients, the researchers noted.

However, "the unique value of this study lies in the homogeneity of the patients with H1N1-related ARDS and the matching methods used," they said. The consistency of the results across all three matching methods strengthens the role of ECMO in reducing hospital mortality in these patients, they said.

The SwiFT study was supported by the U.K. National Institute for Health Research. Dr. Noah had no financial disclosures, but several coauthors received reimbursement or grants from pharmaceutical companies and institutions. ■

COMMENTARY

Dr. Carl A. Kaplan, FCCP, comments: As we enter the 2011-2012 influenza season, the controversy relating to ECMO in ARDS is still fresh on everyone's minds from the 2009-2010 influenza A(H1N1) pandemic. This was a nonrandomized cohort study in the United Kingdom of patients with ARDS presumed or proven to be associated with H1N1 who were referred and transferred to four specialized ECMO centers. Mechanical ventilation during ECMO was with a low FIO_2 of 0.30, low stretch with peak pressures of less than 30 cm H_2O (ideally 25), and PEEP of 10-15 cm H_2O, all consistent with a lung protective strategy. The primary outcome was survival to hospital discharge analyzed by intention to treat. Of 80 patients, 22 died (27.5%) with only 69 of the patients actually receiving ECMO.

A limitation of this study, which is similar to the other two 2009 publications on ECMO with ARDS during the 2009 influenza A(H1N1) pandemic, is that ECMO clinical care was performed at uniquely selected specialized ECMO centers of excellence with well-trained, experienced, and highly knowledgeable teams. Was the care and the associated outcomes due to the unique care of ARDS at these four specialized centers or specifically due to ECMO?

A major limitation of the study was highlighted in the comment section of the article, namely that the management of the non-ECMO referred patients was not part of the study protocol. Therefore, it was "not possible to ascertain whether lung protective ventilation was used." And the accompanying editorial to the article stated that "use of low tidal volumes remains the only proven therapy to decrease mortality in ARDS." The review of ECMO as it relates to mortality must be clearly compared unambiguously to the current clinical gold standard of high-value evidence-based medicine, which is the low-tidal-volume strategy as defined by the NHLBI ARDS Net Protocol. We need a prospective randomized, controlled study comparing ECMO to the low-tidal-volume lung protective strategy based on the ARDS Net protocol at established ECMO centers. And if it is successful, then the economics of care have to be worked out for the U.S. health care system.

Drug Shortages Increasingly Take Toll on Care

BY ELIZABETH MECHCATIE
Elsevier Global Medical News

SILVER SPRING, MD. – With their increasing prevalence, drug shortages have led to delays in treatment, forced the use of less effective alternatives, and encouraged a burgeoning gray market that sells tough-to-obtain medications at highly inflated prices, according to stakeholders gathered at a recent Food and Drug Administration meeting.

Shortfalls in drug supply have increased in the United States, with 178 shortages of products reported in 2010, up from 61 in 2005, according to Dr. Edward Cox, coordinator of the FDA's drug shortage program. Disproportionately affected are generic drugs and sterile injectable products; the latter accounted for two-thirds of the shortages last year. About half of the injectable shortages were caused by problems with product quality, followed by manufacturing delays (21%) and discontinuations (11%), and other issues including an increase in demand created by another shortage, he said at the meeting.

A June 2011 survey of 820 nonfederal, short-term, acute care hospitals by the American Hospital Association found that almost 99% had experienced one or more drug shortages in the first 6 months of 2011; 44% reported at least 21 shortages during that time. Nearly half reported experiencing drug shortages on a daily basis, 40% weekly, and 13% monthly.

Almost all these hospitals had shortages of surgical anesthesia (95%), followed by drugs used for emergency care (91%), cardiovascular care (90%), GI/nutrition (89%), pain management (88%), infectious disease (83%), and oncology (66%).

Drug shortages have hit the fields of oncology and anesthesiology particularly hard, causing delay or postponement of clinical trials of cancer treatments.

Dr. Len Lichtenfeld, deputy chief medical officer of the American Cancer Society, noted that many generic cancer drugs are in short supply. Such drugs, developed years ago, often are inexpensive and "remain mainstays of many currently available and effective cancer treatment programs," he said. Generic cancer drugs that are in short supply include fluorouracil (5-FU), paclitaxel, daunorubicin, cytarabine, bleomycin, and cisplatin.

In many cases, such shortages are causing patients to have to travel further to get the drugs they need. Alternatively, they are treated with second- and third-line therapies that are not necessarily as effective, Dr. Lichtenfeld said. Many adult and pediatric trials of cancer treatments have been suspended when supply of the active control drug is no longer available, he added, and ACS is regularly contacted by patients and families who are looking for medications in short supply.

Exacerbating a shortage situation is the emergence of gray markets that trigger hoarding, he said.

Substitute drugs can often be more expensive and involve additional labor costs, adding up to an estimated $415 million annually, according to Bryant Mangum, vice president of pharmacy services at Premier Healthcare Alliance, a network of over 2,500 hospitals in the United States. An analysis of 636 unsolicited sales offers from gray-market vendors conducted by Premier found that the average markup of a drug price was 650%. The greatest markups were for drugs used in critical care sedation and surgery, chemotherapy, emergency care, and anti-infective drugs, he said. Almost half the drugs were marked up by at least 1,000%, more than 25% were marked up by at least 2,000% – and a drug used to treat hypertension that usually costs $25.90 was being offered at $1,200, "a staggering increase," he said at the meeting.

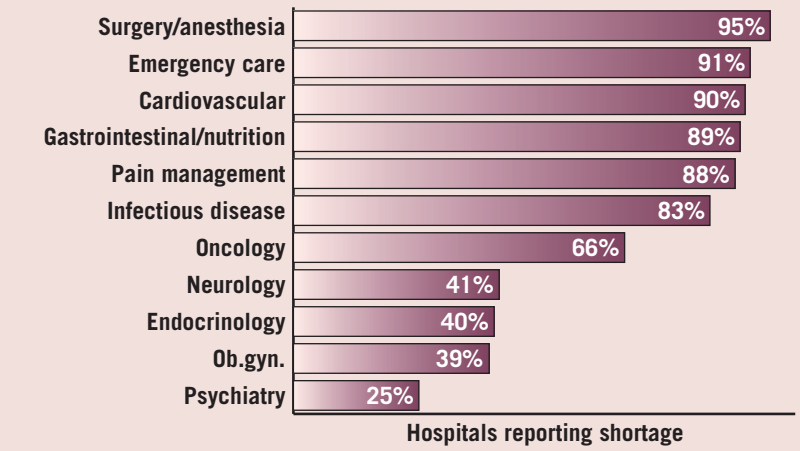
Manufacturers have been giving the FDA earlier notification about the potential for supply issues, a strategy that the agency says has successfully head off some shortages (see story below). In rare cases, the FDA allows a product from an unapproved source to be imported into the U.S. temporarily, which was the case for foscarnet, norepinephrine, leucovorin, and capecitabine.

Other recommendations for resolving, preventing, and alleviating drug shortages include creating stockpiles of certain drugs, similar to vaccine stockpiles; developing guidelines on treatment alternatives when there is a shortage of a drug, such as an antibiotic; and improving communications about drug shortages between FDA and stakeholders.

Clinicians need to be notified faster about shortages so they can be better prepared, according to several practicing physicians who spoke at the meeting. Of the hospitals surveyed by the AHA, 70% responded that the available information on how to manage drug shortages was not adequate. Sources for such information include the American Society of Health-System Pharmacists, the FDA drug shortage website, and direct communication with manufacturers.

Dr. Cox and Mr. Mangum had no disclosures. Dr. Lichtenfeld said that he owns Johnson & Johnson stock and that the ACS receives grants from pharmaceutical companies. ■

Drug Shortages Reported Across All Treatment Categories



Note: 820 acute care hospitals responded to a survey conducted June 1-22, 2011.
Source: American Hospital Association

ELSEVIER GLOBAL MEDICAL NEWS

Executive Order Aims to Help Alleviate Drug Shortages

BY ALICIA AULT
Elsevier Global Medical News

President Obama on Oct. 31 issued an executive order calling on manufacturers to be more proactive in reporting pharmaceutical shortages to the Food and Drug Administration.

The order does not give the FDA any additional authority. Rather, "it will marshal all the resources and regulatory power we already have to make sure Americans don't leave pharmacies empty handed," Kathleen Sebelius, Health and Human Services secretary, said during a press briefing.

The "announcement today enhances and amplifies efforts we are already undertaking at FDA to monitor and prevent and respond to drug shortages," FDA Commissioner Margaret Hamburg said during the briefing.

Currently, drug makers are required to notify the FDA of an impending shortage if they are a sole-source producer or if the drug is for a life-threatening condition or a life-sustaining treatment, Dr. Hamburg said. The executive order directs the agency to broaden reporting so that it covers more drugs and to further expedite review of new manufacturing sites, drug suppliers, and manufacturing changes.

THE DEPARTMENT OF JUSTICE WILL HAVE MORE AUTHORITY TO INVESTIGATE POTENTIALLY EXPLOITATIVE PRICING OF PRODUCTS IN SHORT SUPPLY.

According to the FDA, the number of reported drug shortages has tripled from 61 in 2005 to 178 last year. The agency issued a report Oct. 31 outlining the shortage issue and its response. Of 127 shortages that were reported in 2010-11, 80% were for sterile injectables, including oncology drugs, antibiotics, and electrolyte/nutrition drugs. The agency found that the main reasons for the reported shortages were problems at the manufacturing facility (43%), delays in manufacturing or shipping (15%), and active pharmaceutical ingredient shortages (10%).

Shortages continue to be a significant problem. More than 80% of respondents to a recent poll by the Oncology Report said that shortages were affecting their prescribing.

Some shortages have been caused when a manufacturer simply decided to exit the market. But a separate analysis by the Health and Human Services department found that profits were not a key reason for shortages, at least for oncology drugs, Sherry Glied, Ph.D., HHS assistant secretary for planning and evaluation, said during the briefing.

The main issue in oncology is that there's a greater demand for generics than there is supply, Dr. Glied said.

Dr. Hamburg said that the executive order would help if it spurs manufacturers to notify the agency earlier of impending shortages. The agency prevented 38 shortages in 2010, and 99 so far this year, in part because the manufacturer and the FDA were more proactive, she said.

In a third of the shortages, the agency asked a company to increase production. In 28% of cases, the FDA worked with manufacturers to identify ways of mitigating quality issues by being more flexible, and review of regulatory submissions was expedited in 26% of cases.

In addition to the executive order, the administration took several other steps to address shortages. The FDA sent a letter to drug makers reminding them of their legal responsibility to report the discontinuation of certain drugs and urged more voluntary reporting.

The White House also said that it would give the Department of Justice more authority to investigate potentially exploitative pricing of products in short supply.

The FDA will also double the size of its Drug Shortages Program, from 5 to 11 people, Dr. Hamburg said. She noted that the agency also uses staffers from other divisions to help address shortages.

The White House endorsed legislation that would give the FDA even greater monitoring and enforcement activity. The Preserving Access to Life-Saving Medications Act (S. 296) was introduced in February by Sen. Amy Klobuchar (D-Wisc.) and Sen. Bob Casey (R-Pa.).

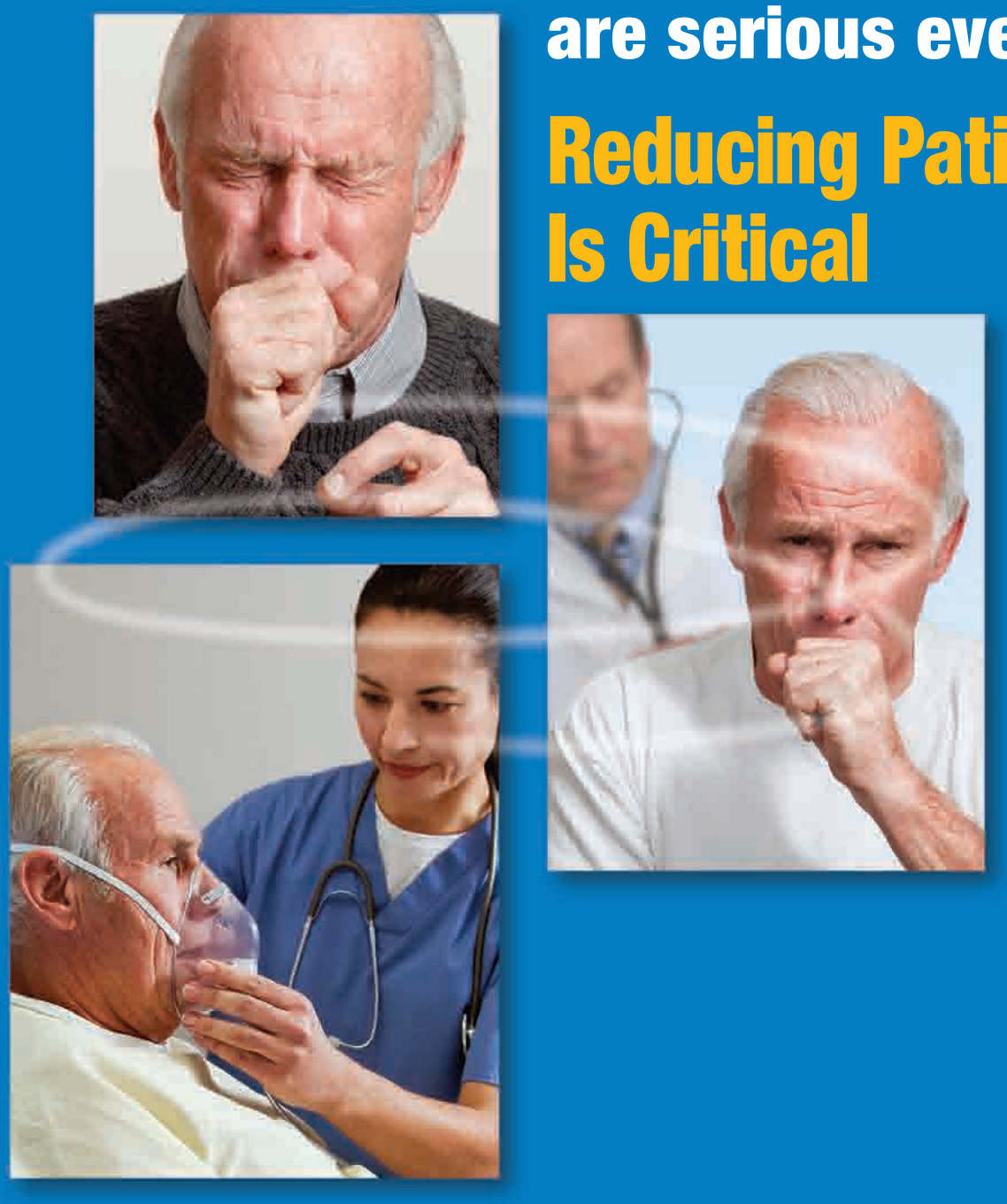
At press time, the bill had 17 Senate cosponsors. Its House companion, H.R. 2245, was introduced in June by Rep. Tom Rooney (R-Fla.) and Rep. Diana DeGette (D-Colo.); that bill has 46 cosponsors. ■

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.

NEW
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

INTRODUCING 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 new class of drugs 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.

NEW

Daliresp®

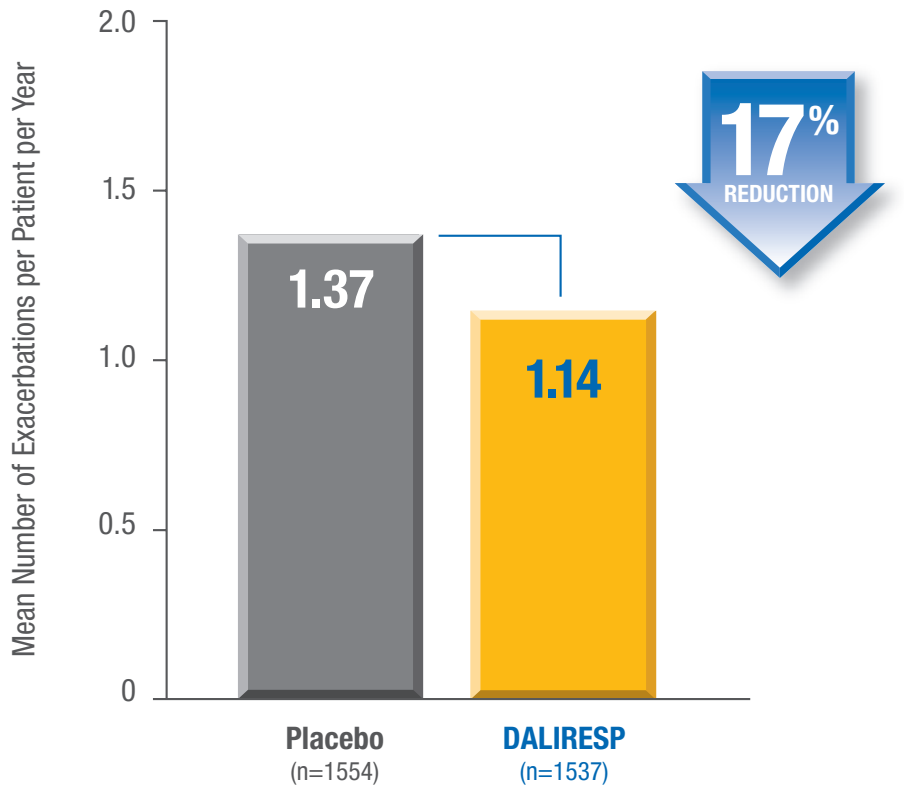
(roflumilast) tablets

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 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 June 22, 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 July 21, 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 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.

NEW Daliresp® (roflumilast) tablets 500 mcg

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

 84-12000156T 09/11

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.

Manufactured by:
Nycomed GmbH
Production Site Oranienburg
Lehnitzstrasse 70 – 98
16515 Oranienburg
Germany

Manufactured for:
Forest Pharmaceuticals, Inc.
Subsidiary of Forest Laboratories, Inc.
St. Louis, MO 63045, USA

Rev 2/2011

84-1020598-BS-T-RMC17137-FEB11

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

Celebrating Diversity Within the ACCP

BY DR. SOLA OLOPADE, MPH, FCCP; AND DR. MARILYN FOREMAN, MS, FCCP
Co-Chairs, ACCP Diversity Committee

Despite the technologic advances of the last 3 to 4 decades, which have improved life expectancy especially in developed countries, health disparities continue to widen both locally and globally with negative consequences that cannot be further ignored. In October 2010, Dr. David Gutterman, FCCP, became president of the American College of Chest Physicians (ACCP) and conveyed his commitment to fostering diversity and addressing disparities in cardiopulmonary, critical care, and sleep medicine during his presidential address. To institutionalize his vision, he created the ACCP Presidential Task Force on Diversity and named Dr. Marilyn Foreman, MS, FCCP, Morehouse School of Medicine, Atlanta, Georgia, as chair and Dr. C. Sola Olopade, MPH, FCCP, University of Chicago, Chicago, Illinois, as co-chair. The CHEST Foundation, the supporting foundation of the ACCP, provided staff leadership and support. The charge to the group was to critically evaluate the scope of diversity within the College and explore opportunities for innovative approaches to foster diversity and inclusiveness in all College activities and promote health equity.

Over the 8-month term of the task force, important changes that have been implemented following approval of the ACCP Board of Regents include revision of the ACCP mission and vision statements and the creation of the ACCP Diversity Committee. The major focus areas for the diversity committee include the following: (1) revision of the ACCP fellowship pledge, which has been completed and is awaiting final approval by the Board of Regents; (2) suggesting strategies for promoting diversity and inclusiveness in the ACCP leadership development plan, recruitment for board positions, and assignment to key committees; (3) advice on how to leverage existing relationships and strategic alliances to enhance diversity and eliminate disparities within the ACCP; (4) integration of diversity within ACCP educational activities; and (5) provision of input on restructuring of the NetWorks.

Through this visionary leadership by the president, and with support of the ACCP Board of Regents, the College has demonstrated leadership and commitment to issues of diversity that will serve as a model for other societies. There is great potential and opportunity to work with local, regional, and global organizations committed to similar goals, such as the American Medical Association's Commission to End Health Care Disparities, minority medical societies, and minority medical student, women's health, and allied health organizations. The committee will also promote the efforts of the College to reduce respiratory health disparities related to age, gender, race, and sexual orientation.

Dr. Sheila Goodnight-White, FCCP, chair of the Women's Health NetWork; Dr. Liziamma George, FCCP, past chair of the Cultural Diversity NetWork; Dr. Stephanie Levine, FCCP, chair of The CHEST Foundation's Awards Committee; Dr. LeRoy Graham, FCCP, regent-at-large member of the Board of Regents; Dr. Susan Millard, FCCP, member of the Marketing Committee; Dr. Jay Peters, FCCP, incoming chair of the Council of NetWorks; and Dr. Kalpalatha Guntupalli, FCCP, Past President of the College, all bring their varied interests and expertise to the committee.

The committee is grateful to ACCP President Dr. David Gutterman, FCCP; Past President Dr. Allen Goldberg, MBA, Master FCCP; Past President Dr. Alvin Thomas Jr, FCCP; Donna Gardner, RRT; Dr. Philip Marcus, MPH, FCCP; Dr. Angeline Lazarus, FCCP; Dr. Wickii Vigneswaran, FCCP; Dr. Walfredo Leon, FCCP; and Marilyn Lederer for their service on the task force, which resulted in the development of this committee and its ambitious agenda. We welcome the input of the membership and request that suggestions for focus areas are sent to Jenny Nemkovich at jnemkovich@chestnet.org. ■

Update on Pulmonary Function Coding for 2012

BY DR. EDWARD DIAMOND, FCCP

The 2012 CPT® codes include significant revisions in the area of pulmonary function testing (codes **94010-94799**) with multiple code deletions and multiple new codes. These changes will not take effect until January 1, 2012. The PFT codes commonly performed and billed together were consolidated into single codes to eliminate payments for duplicative work.

As in the past, if a separate identifiable Evaluation and Management (E/M) service is performed, the appropriate E/M code may be reported in addition to codes **94010-94799**. For example, when spirometry (**94010**) is performed on the same day as an office visit for an established patient who meets documentation requirements for code **99214**, both **94010** and **99214** would be reported. The appending of a **25** modifier to the E/M code is not necessary; however, many providers include it because it may be required by private payers. The five-digit numeric CPT code represents the global service that includes both the technical and professional (interpretation) components. A **26** modifier is added when reporting only the professional (interpretation) service, and a **TC** modifier is added when reporting only the technical service. For example, code **94010** describes the global service provided by a physician who performs spirometry in a private office. The physician must bear all costs (clinical staff, medical supplies, equipment) associated with the testing. If a physician interprets a test performed in a hospital-based laboratory, the physician reports the professional component (**94010-26**), and the

Continued on following page

CPT Code Descriptors for Four New 2012 PFT Codes

94726 Plethysmography for determination of lung volumes and when performed, airway resistance (Do not report **94726** in conjunction with **94727, 94728**)
94727 Gas dilution or washout for determination of lung volumes and, when performed, distribution of ventilation and closing volumes (Do not report **94727** in conjunction with **94726**)
94728 Airway resistance by impulse oscillometry (Do not report **94728** in conjunction with **94010, 94060, 94070, 94375, 94726**)
+94729 Diffusing capacity (eg, carbon monoxide, membrane) (List separately in addition to code for primary procedure) (Report **94729** in conjunction with **94010, 94060, 94070, 94375, 94726-94728**)

Deleted PFT Codes

Deleted 10 PFT Codes: 93720, 93721, 93722, 94240, 94260, 94350, 94360, 94370, 94720, 94725.
(**93720-93722** Plethysmography codes have been deleted. To report, use **94726**)
(**94240** Residual Lung Capacity has been deleted. To report, see **94726**, **94727**)
(**94260** Thoracic Gas Volume has been deleted. To report, see **94726**, **94727**)
(**94350** Lung Nitrogen Washout Curve has been deleted. To report, see **94726**, **94727**)
(**94360** Measure Airflow Resistance has been deleted. To report, see **94726**, **94728**)
(**94370** Breathe Airway Closing Volume has been deleted. To report, see **94726**, **94727**)
(**94720**, **94725** Diffusing Capacity codes have been deleted. To report, see **94729**)

Continued from previous page

hospital reports the technical component (**94010-TC**). The 2012 revisions eliminate a current exception to this pattern. The new code **94726** for plethysmography replaces the deleted codes **93720**, **93721**, and **93722**.

The tables identify the 2012 accepted pulmonary function testing codes and the deleted codes. The intent of the changes is to simplify some areas that were unclear and bundle codes to avoid double payment for two tests with common components of preservice and postservice times.

The 10 codes from 2011 being deleted for 2012 are the following: **93720, 93721, 93722, 94240, 94260, 94350, 94360, 94370, 94720,** and **94725**. Some of the significant changes include the replacement of **94360** (airway resistance) with **94728** (airway resistance by impulse oscillometry) that can be reported only separately. There will be no separate reimbursement for airway resistance measured by body plethysmography (**94726**). Code **94260** (thoracic gas volume) will be eliminated because the appropriate use of this code has been unclear, and it is included in **94726**, **94727**. Diffusing capacity (**94729**) replaces **94720**, and **94725** is an add-on code to **94010**, **94060**, **94070**, **94375**, and **94726-94728**. ■

Update on Bronchoscopy Coding for 2012

BY DR. ALAN L. PLUMMER, FCCP

Over the past decade, many new codes have been created for pulmonary medicine. Most have been new codes for bronchoscopy procedures. For 2012, there are two new Category III CPT® codes for bronchial thermoplasty. **0276T** should be used for bronchoscopy with bronchial thermoplasty of one lobe. **0277T** should be used for bronchoscopy with bronchial thermoplasty of two lobes. They are Category III codes, so they have no physician work values and no specific reimbursement. They are to be used for tracking purposes, so data can be collected to assist pulmonary RUC advisors in applying for Category I status when the time is right. Achieving Category I status would necessitate the codes being surveyed by the RUC. At the RUC, the codes would be assigned physician work values plus practice and liability expense values then sent to the Centers for Medicare and Medicaid Services (CMS) for approval. Once the codes have been approved by the CMS, they will be reimbursed by Medicare.

If Category III codes do not achieve Category I status within 5 years, those codes would sunset and would not be able to be used afterward. This again emphasizes the need to use these new bronchial thermoplasty codes, so Category I status for these codes can be achieved within the 5-year limit.

Currently, when bronchial thermoplasty is performed, the unlisted code **31899** (unlisted code for bronchial procedures) must be used on the claim form. A practice-determined charge should be added to the claim form, and a detailed description of the bronchial thermoplasty procedure should accompany the claim when it is submitted. In 2012 and thereafter, when bronchial thermoplasty is performed, codes **0276T** and **0277T** should be reported.

A practice-derived fee for these codes can be submitted with the claim to request reimbursement. For example, one could submit a charge similar to your charge for **31641**. In 2012, it will **not** be appropriate to use code **31899** (unlisted code for bronchial procedures) for bronchial thermoplasty.

For practice management issues or questions on coding, please contact Marla Brichta at (847) 498-8364 or mbrichta@chestnet.org. ■

DR. PLUMMER *is the author of Chapter 9 of* Coding for Chest Medicine 2011.

2012 CPT Category III Bronchial Thermoplasty 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: It is important to encourage physicians to report tracking codes that help us provide data for our request to transition to a CPT Category I code and having the code subsequently valued and paid.

ACCP Partners to Develop COPD Guidelines

BY SANDRA ZELMAN LEWIS, PHD; DR. DARCY MARCINIUK, FCCP; AND DR. NICOLA A. HANANIA, MS, FCCP

Guidelines on the *Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease (COPD)* were published in the August 2, 2011, issue of the *Annals of Internal Medicine*.[1] The American College of Chest Physicians (ACCP) jointly partnered in the development of these guidelines with the American College of Physicians, American Thoracic Society, and European Respiratory Society. ACCP representatives on the guideline panel included Dr. Darcy Marciniuk, FCCP, and Dr. Nicola A. Hanania, MS, FCCP, who also co-authored an editorial about these joint guidelines in the September issue of *CHEST*.[2]

The comprehensive literature search and evidence review was conducted with a focus on the value of spirometry for screening and diagnosis of COPD in adults who are asymptomatic with risk factors, and the efficacy and comparative effectiveness of management strategies, including inhaled monotherapies (eg, anticholinergics, long-acting beta-agonists, corticosteroids), combination pharmacologic therapies, and pulmonary rehabilitation. The value of the patient history and physical examination as a reliable predictor of airflow obstruction was also examined.

These guidelines mark a significant advance in the field of evidence-based medicine such that organizations that might otherwise develop competing guidelines agree to work collaboratively in the interest of developing one set of harmonized guidelines. It can be difficult for physicians and other health-care providers to choose among competing guidelines, and the developers of such guidelines do them a disservice. Harmonized guidelines rise to the level of the most rigorous standards that can be mutually achieved, thus raising the bar for guideline developers and the field overall. In the end, it is the patients that benefit the most.

The ACCP is currently partnering with several organizations on future guidelines in other clinical areas. Although not all ACCP guidelines will include equal partnerships, ACCP guidelines benefit from invited representatives from related organizations relevant to the guideline topic. The ACCP is working hard to produce the very best clinical guidelines in its field.

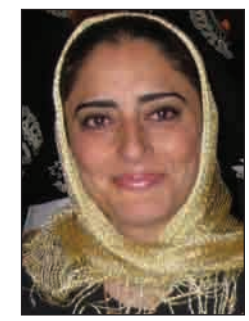
For more information, contact Sandra Zelman Lewis, PhD, at slewis@chestnet.org. ■

1. Qaseem A, Wilt TJ, Weinberger SE, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. Ann Intern Med. *2011;155(3):179-191.*

2. Hanania NA, Marciniuk DD. A unified front against COPD: clinical practice guidelines from the American College of Physicians, the American College of Chest Physicians, the American Thoracic Society, and the European Respiratory Society. Chest. *2011;140(3):565-566.*

Meet the New Ambassadors Group Chair

For the past 10 years, the Ambassadors Group has conducted activities that use a broad range of talent and expertise of their members. These activities have included education programs targeted to improving lung health and fund-raising in support of humanitarian efforts in The CHEST Foundation's priority areas. Committed leaders are key to the accomplishments and impact of the Ambassadors. Dr. Sabiha Raoof, FCCP, embraces the opportunity to serve as the Ambassadors Group chair. She brings expertise as a physician, knowledge gained from other Ambassadors Group members, and a desire to expand the group's reach.



DR. SABIHA RAOOF, FCCP

Dr. Raoof is Chair, Department of Radiology for Jamaica Hospital Medical Center and Flushing Hospital Medical Center in New York. She is the wife of Dr. Suhail Raoof, FCCP, 2011-2012 ACCP President. Her daughter, Sana, is a senior at Harvard, and her son, Sahir, is a freshman at Columbia. In addition to her busy career and family life, Dr. Raoof enjoys gardening, reading, and traveling.

Dr. Raoof first became involved with the Ambassadors Group through a friend who encouraged her to attend the group's activities during CHEST. She enjoys the friendships she has made, as well as attending special Ambassadors Group programs, such as the "Celebrating Our Diversity" presentation of international Ambassadors featured each year at CHEST.

Dr. Raoof would like to see the Ambassadors Group build upon the efforts to teach young people about the risks of tobacco use and broaden the message regarding all the ways they can take care of their lungs. Among her aims for the Ambassadors Group are increasing membership, fostering the involvement of high school and college student members, enhancing communication among Ambassadors, and growing the group internationally. Dr. Raoof believes that aligning with The CHEST Foundation's OneBreath™: Make The Most Of It campaign will further the support of these aims.

Dr. Raoof encourages all ACCP members and their families to join the Ambassadors Group. She notes, "There is so much to learn from this diverse group. I have learned from the many Ambassadors who use their creativity to present Lung Lessons℠ to students, as well as from others who champion good lung health with their enthusiasm and positive approach."

More information about the Ambassadors Group and Lung Lessons℠ is available in the "Community" section of OneBreath.org. ■

This Month in *CHEST*: Editor's Picks

BY DR. RICHARD S. IRWIN, MASTER FCCP

POINT/COUNTERPOINT EDITORIAL

▶ **Will Public Reporting of Health-care Quality Measures Inform and Educate Patients?**
Yes. Dr. M. L. Metersky, FCCP
No. Dr. J. T. Kullgren; Dr. R. M. Werner

ORIGINAL RESEARCH

▶ **Factors Associated With Bronchiectasis in Patients With COPD.** *By Dr. M. Martinez-Garcia et al.*

▶ **Depression Is More Common in Girls With Nonatopic Asthma.** *By Dr. S. Bahreinian et al.*

▶ **Does Propulsion Mechanism Influence the Long-term Side Effects of Oral Appliances in the Treatment of Sleep-Disordered Breathing?** *By Dr. J-P Vezina et al.*

RECENT ADVANCES IN CHEST MEDICINE

▶ **Thoracic Ultrasonography for the Pulmonary Specialist.** *By Dr. S. J. Koenig et al.*

SLEEP STRATEGIES

Teenagers and Sleep

Sleep disturbances are common during the teenage years. The two most common sleep problems noted are behaviorally induced insufficient sleep and delayed sleep phase.

Additionally, given the obesity epidemic, obese teenagers are also at risk for development of obstructive sleep apnea, and they may manifest symptoms of this sleep disorder.

Rarely, narcolepsy can appear during teenage years; about 50% of patients with narcolepsy have an onset of symptoms during the first decade of life.

In this article, we will discuss the common sleep problems facing teenagers.

Insufficient Sleep

Given the plethora of activities competing for teenagers' time and attention, it can be challenging for them to set aside enough time for sleep. Sleep needs are different in teenagers and adults. Research shows that adolescents require at least as much sleep as they did as children, which is generally 8-1/2 to 9-1/4 h each night (Carskadon et al. *Sleep*. 1980;2[4]:453).

In one study (Noland et al. *J Sch Health*. 2009;79[5]:224), more than 90% of teenagers reported sleeping less than the recommended 9 h. In fact, about 10% of teenagers slept less than 6 h each night.

Multiple factors are responsible for reducing the amount of sleep during the teenage years. For example, the start of the school day is earlier for high school students. Many high school students have to wake up between 5:30 AM and 6:00 AM to get to school on time.

Teenagers also engage in many extracurricular activities, such as sports and clubs. In addition, many high school students are taking honors and advanced-placement classes. In the evenings, along with their homework, many teenagers may be working part-time jobs to earn money for college. The Internet, computers, smartphones, video games, and other electronic gadgets compete for their attention.

Also, there is decreased control exercised by parents regarding teenagers' sleep schedules. Unfortunately, teenagers often give a lower priority to sleep than do adults. Many teenagers try to compensate for this by sleeping in on weekends and during vacations.

There are many consequences of sleep restriction in teenagers. Nine hours of sleep, and sometimes more, is necessary for teenagers to maintain optimal alertness during the daytime. Lack of sufficient sleep affects cognitive function and leads to difficulty concentrating and learning. Teenagers may have difficulty staying awake in class.

Lack of sleep also leads to behavioral problems, such as depressed mood and irritability, which can adversely affect interpersonal relationships and communication skills.

There is literature (Van Cauter and Knutson. *Eur J Endocrinol*. 2008;159[suppl 1]:S59) showing that sleep deprivation is a risk factor for the development of obesity and other adverse metabolic consequences.

Even more serious is that insufficient sleep increases the risk of drowsy driving and falling asleep at the wheel, leading to major accidents that can be fatal. Significant sleep loss results in cognitive impairment similar to that caused by alcohol ingestion. Insufficient sleep combined with alcohol in an inexperienced young driver is an especially deadly combination.

MORE THAN 90% OF TEENAGERS REPORTED SLEEPING LESS THAN THE RECOMMENDED 9 H. ABOUT 10% SLEPT LESS THAN 6 H EACH NIGHT.

The only remedy for insufficient sleep by teenagers is getting the recommended amount of sleep. Given the multitude of demands on a teenager's time, it can be a challenge to set aside 9 h of sleep time. Sleep should be regarded as just as vital to body function as food, water, and oxygen.

Doctors, parents, and teachers should emphasize the importance of getting an adequate amount of sleep. Proper planning and prioritization of activities is a good first step in managing time. This includes avoiding last-minute scrambling and "pulling all-nighters." Teenagers should prioritize their extracurricular activities and curb late-night social time. If they are working a part-time job, they should try to limit their number of work hours.

Good sleep hygiene practices should be emphasized that encourage adherence to a regular sleep schedule and going to bed and getting up at the same time every day, regardless of whether it is a weekday or weekend.

If teenagers are drowsy during the day, they can consider a short nap of 25 to 30 min after school that can be refreshing and improve their functioning. They should be careful not to take longer naps because that can make it more difficult to fall asleep at night.

Caffeinated beverages may help teenagers stay awake during class, but they should avoid caffeinated beverages after 2:00 PM in the afternoon because caffeine can interfere with sleep onset at night.

Nicotine is a powerful stimulant, and discouraging teens from smoking will also help promote sleep.

Exercise close to bedtime should be avoided. The bedroom environment should be sleep promoting with cool temperature and no bright lights or loud noises.

Stimulating activities such as television, loud music, video games, surfing the Internet, and text messaging should be avoided an hour or two before bedtime. If teenagers have a hard time doing this, turning the television and other electronic gadgets off or removing them from their rooms is an extreme option.

Winding down at night with a warm shower, reading a book, or listening to soft music can help promote sleep.

Delayed Sleep Phase

In the last few decades, there has been a growing awareness of the changes in sleep patterns as children transition to adolescence. There is a normal propensity for small delays of the sleep-wake schedule and circadian phase during adolescence.

The exact mechanism of this circadian phase delay during adolescence is unclear. Carskadon and colleagues (*Sleep*. 1998;21[8]:871) found that mature adolescents had later circadian rhythm timing based on melatonin secretions in saliva samples.

Melatonin secretion occurs at a later time in adolescents as they mature; thus, it was difficult for them to go to sleep earlier at night. The melatonin secretion also turns off later in the morning, which made it harder for adolescents to wake up early.

The change in the circadian clock delays the time teenagers start feeling sleepy, often until 11:00 PM or later, and it also delays their wake-up time. There are social and behavioral factors that aggravate this delay in adolescents. Social and behavioral factors (eg, evening social activities, staying up late to do homework, watching television, surfing the Internet, playing video games) also favor the delay of the sleep-wake schedule.

Due to early morning classes, most teenagers have to wake up between 5:30 AM and 6:00 AM. This leads to two problems: (1) insufficient sleep because it is difficult to get 9 h of sleep, and (2) significant difficulty waking up. It is difficult for the teenagers to wake up because they are trying to wake up around the most "sleepy" circadian time. This leads to excessive daytime sleepiness and difficulty paying attention in class.

Some of the strategies to manage the delayed sleep phase in teenagers are to maintain a regular sleep schedule and maintain good sleep hygiene practices as described previously.

Light is the primary synchronizing or entraining agent (zeitgeber) for the circadian clock, so lighting strategies should help with circadian clock alignment to the day-night cycle.

Studies have shown that the circadian timing system can be reset if light exposure is carefully controlled. Hence, dimming the lights as bedtime approaches and turning off the lights during sleep should be considered. Bright light exposure during morning should be encouraged.

Starting school at a later time is a strategy that has been explored in some school districts. Studies from Minnesota and Massachusetts school districts have shown that teenagers who attended schools with later start times were able to sleep about 1 h longer and were more alert during school.

In a Kentucky school district, later school start times increased the sleep time of adolescents and decreased their risk of motor vehicle crashes (Danner and Phillips. *J Clin Sleep Med*. 2008;4[6]:533).

Changing a school's start and end time to be later for teenagers is not an easy undertaking. Factors that can be adversely impacted by such a change include school transportation schedules, schedules of younger students, after-school activities, teachers' free time, and family schedules.

There are multiple stakeholders involved in such a decision—students, teachers, parents, principals, counselors, administrators, school boards, and the community.

Sleep specialists can play an important role by educating school administrators about the potential adverse outcomes of very early school start times.

Hopefully, in the near future, increased awareness of the sleep problems faced by teenagers should motivate schools across the country to synchronize school schedules with students' circadian clocks. That way, teenagers are in school during their most alert hours to achieve their full academic potential.

In summary, teenagers have a different set of sleep problems that should be promptly recognized and addressed to improve their overall health and well-being. ■

Dr. Saiprakash B. Venkateshiah, FCCP
Assistant Professor
Emory University School of Medicine
Atlanta, Georgia

CLASSIFIEDS

Also available at www.imngmedjobs.com

PROFESSIONAL OPPORTUNITIES

Division Chief, Pediatric Pulmonology

Phoenix Children's Hospital is seeking a **Chief of Pediatric Pulmonology.** The desired candidate should be a board certified pediatric pulmonologist with demonstrated excellence in administration, clinical care, teaching and academics. The successful candidate should also have strong leadership and interpersonal communication skills.

Phoenix Children's Hospital is the only free-standing children's hospital in the state of Arizona, located in the fifth largest metropolitan region in the country. Phoenix Children's Hospital just completed a major physical expansion growing its licensed beds to 600 with the opening of a new, state of the art inpatient facility. In addition, brand new, luxurious ambulatory space has also been developed to meet our growing numbers of children.

The new division chief will have the opportunity to mentor our six current physicians, expand the hospital's current Cystic Fibrosis and Sleep programs, identify and develop new programs, and recruit faculty to help achieve the institutional goals of pursuing a fellowship and collaborative research. Academic appointments with the University of Arizona College of Medicine Phoenix and the Mayo Clinic are available.

Phoenix Children's Hospital is an equal opportunity employer.

Interested Candidates should contact:

David Bank, MD MBA
Physician in Chief
Phoenix Children's Medical Group

(w) 602-546-1905
(c) 602-361-0359
dbank@phoenixchildrens.com

Phoenix Children's Hospital
1919 East Thomas Rd. Building B, Suite 2310
Phoenix, Arizona 85016

Critical Care Intensivists

The University of Cincinnati Division of Pulmonary, Critical Care and Sleep Medicine has open faculty positions for critical care intensivists at the Assistant Professor level. Primary duties include night coverage at University Hospital of a busy academic medical ICU with 24/7, unit based, fellow and house staff presence. Additional opportunities exist for attending on inpatient and outpatient pulmonary consultation services as well as at the Cincinnati VA Hospital, staffing the VISN 10 TeleICU monitoring center. Interest in clinical teaching and conducting patient oriented research is highly desirable.

Current Ohio medical license and board certification/eligibility in critical care medicine is required. Additional pulmonary medicine board certification/eligibility is optimal.

Please send a cover letter and curriculum vitae to the attention of David Norton, M.D., MICU Director, 231 Albert Sabin Way, MSB 6053, Cincinnati, OH 45267-0564, or email **david.norton@uc.edu**

For Deadlines and More Information Contact:
Rhonda Beamer
443-512-8899 Ext 106
FAX: 443-512-8909
Email: **rhonda.beamer@wt-group.com**

BC/BE Pulmonary/ Critical Care Physician

Well-established, successful group practice in Sacramento, California seeks well-trained, energetic BC/BE pulmonary/ critical care physician with emphasis in infectious diseases. Excellent ICU program. Competitive compensation package.
E-mail CV and cover letter to
mfwong@vortran.com

Pulmonary/Critical Care Physician Metro Atlanta

Established, 18-physician Pulmonary Medicine practice in suburban Atlanta, looking for a BC/BE Pulmonary/Critical Care Physician. Sleep certification a plus. Practice includes all aspects of pulmonary medicine including; critical care, sleep medicine, pulmonary rehab, clinical research, and interventional pulmonology. Practice located at three large acute-care hospitals. Practice has a team of 14-advanced practitioners. Competitive salary with aggressive bonus structure. Malpractice coverage and generous benefits package including 403b and defined pension plan. Please contact
Provider.Positions@wellstar.org
or 770-792-7539.

New York - Nassau County, Long Island

Hospital Affiliated-Private Practice seeking FT and PT BC/BE Pulmonologist. Successful candidate(s) to join our existing five Physician single- specialty group. We offer a generous mix between office, hospital and a nursing home based practice, we are affiliated with a large university hospital and provide services at local community hospitals as well. Practice includes Directors of a large ventilator unit, critical care, medicine, sleep and pulmonary departments. We are also affiliated with two state of the art sleep labs and rehabilitation centers. We offer a competitive salary, excellent benefits and on call schedule. Our practice offers a balanced lifestyle. Immediate openings are available as well as openings for July 2012. This is not a J-1 visa opportunity. Motivated, qualified candidates should fax CV to 516-796-3205 c/o Cindy Strain or email to: **Cyndy65@aol.com** Call 516-796-3700 for further information on this exciting opportunity.

Disclaimer

Chest Physician assumes the statements made in classified advertisements are accurate, but cannot investigate the statements and assumes no responsibility or liability concerning their content. The Publisher reserves the right to decline, withdraw, or edit advertisements. Every effort will be made to avoid mistakes, but responsibility cannot be accepted for clerical or printer errors.

Pulmonary/ Critical Care/ Sleep Medicine

Excellent opportunity for compassionate and friendly BC/BE physician to join growing Pulmonary/ Critical Care/ Sleep Medicine private practice in Bergen County, NJ. Competitive salary & benefits, Flexible call sharing schedule, productivity bonus.

Please e-mail CV to
lungsdoc@yahoo.com

2011 CLASSIFIEDS

Chest Physician Rates
4 Column Classified Ads
From 1" to 12"
Sizes from 1/48th of a page to a full page

For Deadlines and More Information Contact:
Rhonda Beamer
Walchi Tauber Group, Inc.
2225 Old Emmorton Road, Suite 201
Bel Air, MD 21015
443-512-8899 Ext 106
FAX: 443-512-8909
Email: **rhonda.beamer@wt-group.com**

Burdensome Transitions Common in Final Days

BY MARY ANN MOON
Elsevier Global Medical News

Nearly one in five patients with advanced cognitive and functional impairment who are in their final days of life is subjected to a burdensome, potentially unnecessary transition in health care, such as being moved from a nursing home to a hospital, according to a report in the New England Journal of Medicine.

The frequency of such transitions varies widely from between regions of the United States, with rates as high as 37% of the cognitively impaired decedents in some states. And the rate appears to be increasing, said Pedro Gozalo, Ph.D., of the program in public health at Brown University, Providence, R.I., and his associates.

The transfer itself can be traumatic for these easily confused and physically frail patients, and it opens the door to fragmentation of care and medical errors, said the researchers. Once hospitalized, many such people near death are subjected to further disturbances such as insertion of feeding tubes or transfer to an intensive care unit. However, hospitalization is usually avoidable in patients with advanced dementia because most of the medical problems that arise at the end of life are predictable and "can be treated with equal efficacy in the nursing home," the investigators said.

They examined Medicare data covering all nursing home residents in the United States and defined "burdensome transitions" according to interviews with families and the expert opinions of geriatricians and palliative medicine specialists. Such transitions thus included transfers during the last 90 days of life from a nursing home to a hospital, transfers from a nursing home to a hospital and on to a different nursing home, and multiple hospitalizations.

The researchers retrospectively identified 474,829 nursing home residents with advanced dementia who were in their last 120 days of life in 2000-2007. Their mean age was 86 years.

A total of 90,228 of these people (19%) had at least one burdensome transition during their final 90 days of life. This included more than 55,000 who were transferred within hours of their deaths, nearly 13,000 who were transferred from one nursing home to a hospital and then to another nursing home, and more than 38,000 who were hospitalized multiple times, the researchers reported (N. Engl. J. Med. 2011;365:1212-21). The rate of burdensome transitions was lowest in Alaska (2%) and highest in Louisiana (37%). Several other southern states, California, and New York also had high rates. The lowest rates after Alaska's were in upper-Midwest and northwestern states and Hawaii.

The nationwide rate of burdensome transitions rose from 17.4% of decedents in 2000 to 19.6% in 2007.

These transitions were more common among black and Hispanic patients than among whites, among men than women, and among patients who had no advance directive than those who did.

Burdensome transitions were associated with what the researchers identified as several markers of poor end-of-life care, including transfer to an ICU during a patient's final days, referral to hospice care within 3 days of death, the presence of stage 4 decubitus ulcers, and insertion of a feeding tube.

Dr. Gozalo and his colleagues noted that a previous study found that "96% of family members report that comfort is the primary goal of care for their relatives with advanced dementia. Yet as we found, the pattern of transitions among nursing home residents with advanced cognitive impairment is often inconsistent with that goal."

The authors said that financial incentives probably underlie many of the burdensome transitions. "Hospitalization generally qualifies a nursing home resident with Medicaid coverage to receive Medicare payments for skilled services, which reimburse the nursing home at a higher rate. In addition, states' Medicaid payment rates and bed-holding policies that pay nursing homes to keep a bed open for hospitalized residents are associated with increased rates of hospitalization.

"These financial incentives probably result in health care transitions that contribute not only to excessive costs but also to a poorer quality of end-of-life care," the investigators said.

"Ultimately, a decline in burdensome transitions will come about through a combination of improved provider incentives and decision making that elicits and respects the choices of patients," they said.

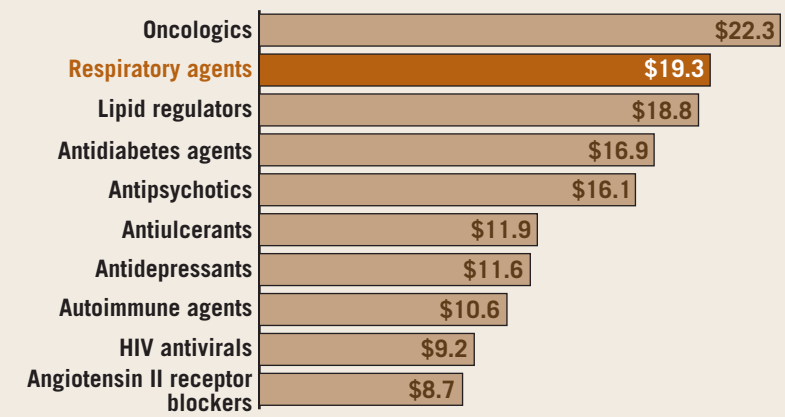
This study was supported by the National Institute on Aging. One of Dr. Gozalo's associates reported being a consultant for the Manor Care nursing home chain and for Point Right, a company that provides information services in long-term care. Another associate reported ties to the Robert Wood Johnson Foundation. ■

COMMENTARY

Dr. Paul Selecky, FCCP, comments: These findings emphasize the importance of advance care planning in dementia patients, including the completion of a POLST document by the patient/family and physician (POLST = Physician Orders for Life-Sustaining Treatment, legal in many states). Early involvement of palliative care follows from the advance care planning.

DATA WATCH

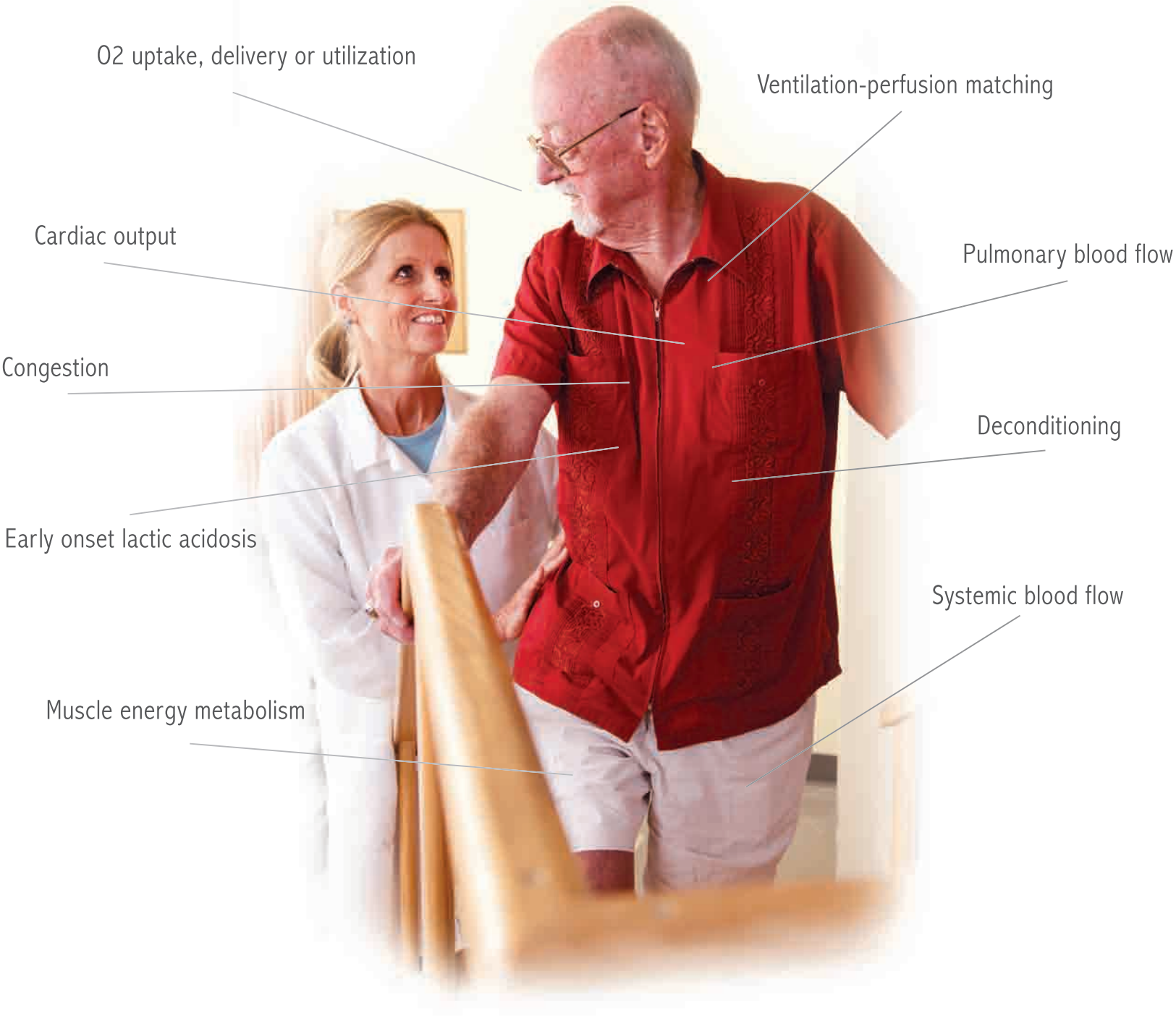
Respiratory Drugs Were the Second–Best-Selling Therapeutic Class in 2010



Note: Figures represent U.S. wholesale revenue in billions.
Source: IMS Institute for Healthcare Informatics

ELSEVIER GLOBAL MEDICAL NEWS

Why is this patient short of breath?



A simple, six-minute in-office test can help you find out with no capital risk to your practice.

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

Learn more by calling 1-888-SHAPE98 (888-742-7398)

or by visiting www.shapemedsystems.com.

SHAPE™