

COURTESY RICK LOCKRIDGE

Michael Stader, RRT, is part of the respiratory team that conducts asthma education and screening events at Atlanta churches.

Outreach Breathes Hope Into Atlanta Communities

BY MELINDA TANZOLA
Elsevier Global Medical News

ATLANTA — Not one more life, says pediatric pulmonologist LeRoy Graham, FCCP.

Not one more life should be taken unnecessarily by asthma and lung disease, and not one more individual should go without the proper medical attention needed to gain control of his or her health.

Experts have grappled for years with the increased asthma morbidity and mortality in minorities, particularly in urban African Americans. Whereas many have suggested various guidelines and strategies to solve the problem, Dr. Graham took to the streets of Atlanta to address the issue head on.

First seeking out a venue through which he could connect with people, Dr. Graham and his colleagues identified African American churches as a viable community resource with which they could partner.

“Black churches have a validated reputation and place within the black community,” Dr. Graham explained. Providing health information and services within this environment can increase people’s willingness not only to receive information, but to actively engage and participate in the health care process. When individuals see that their pastors are supportive of the program, they are significantly more likely to become involved.

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New Year, Same Story: CMS Will Cut Pay 4.6% in '07

Next year’s cuts are ‘tip of the iceberg.’

BY ALICIA AULT
Elsevier Global Medical News

In a not unexpected, but definitely unwelcomed move, the Centers for Medicare and Medicaid Services has announced that it will cut physician pay by 4.6% for 2007.

The federal health program said the scheduled decrease in physician fees is based partly on the fact that spending for physicians’ services rose by 8.5% in 2005, with 7.5% of that rise due to growth in the volume and intensity of physician services.

Physician organizations blame the hit on the sustainable growth rate (SGR). If Medicare spending on physicians increases more than the SGR, CMS must cut physician fees; lower spending means higher rates for physicians.

But errors made in setting the SGR in 1998 and 1999 have led to annual proposed cutbacks and yearly congressional bailouts. Last year, for instance,

medical organizations successfully lobbied Congress to block a proposed 4.4% cut for 2006, but because legislators did not increase fees, payments essentially were frozen at the 2005 rate.

This year, physician groups such as the American College of Chest Physicians again say that they will urge Congress to stop the fee cut and repair the SGR.

“The ACCP’s Government Relations Committee agrees with the MedPAC recommendation that Congress eliminate the SGR and adopt the same approach, based on the Medicare Economic Index (MEI), for physician payment updates that is used for other Medicare providers,” said Dr. Lawrence C. Mohr, FCCP, chair of the committee. “Such an approach would ensure that physician payments reflect the cost of practice.”

“We’ve been strung along by Congress for years now on

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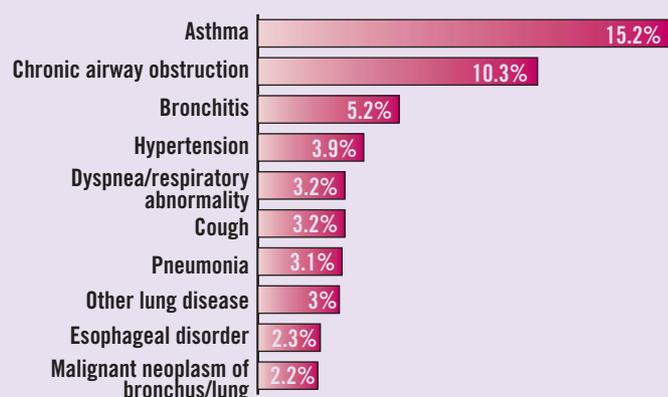


News From the College A ‘Capitol’ Time

This year’s ACCP caucus in Washington brought powerful messages to lawmakers. • 15

VITAL SIGNS

Top 10 Diagnoses by Pulmonologists in 2005



Note: Based on projected nationwide data from a monthly survey of about 70 pulmonologists.
Source: Verispan

IOM: Time to Wake Up to Sleep Disorders

BY DOUG BRUNK
Elsevier Global Medical News

It’s time for physicians and the public alike to wake up to the staggering impact of sleep disorders, a new report from the Institute of Medicine charges.

An estimated 50-70 million Americans suffer from chronic sleep disorders such as insomnia, sleep apnea, and restless legs syndrome, yet the vast majority “go unrecognized because nobody’s asking patients about them,” Dr. Harvey R. Colten, who chaired the committee that assembled the report, said in an interview. “Even when they do [ask], they’re not following up on the problem and dealing with it either directly or by referral. That’s a major issue for the practitioner as well as for the medical educator.”

Titled “Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem,” the wide-ranging report noted that fatigue alone costs an estimated \$150 billion a year in lost productivity and mishaps, and another \$48 billion in medical costs related to motor vehicle accidents that involve drowsy drivers.

Data from the 1990s suggest that sleep disorders themselves cost an estimated \$15.8 billion in

medical costs, a figure the committee believes is conservative.

“What we found was that sleep disorders are extremely common,” said Dr. Allan I. Pack, one of the report’s committee members. “They obviously have an impact not only on sleep and behavior, but in cardiovascular disease and metabolic effects. There really is an unmet public

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Sleep Medicine Report Debuts

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health need," said Dr. Pack, who directs the University of Pennsylvania's Center for Sleep and Respiratory Neurobiology.

The report was commissioned by the American Academy of Sleep Medicine (AASM), the National Center on Sleep Disorders Research of the National Institutes of Health, the National Sleep Foundation, and the Sleep Research Society.

The document comes "at a time when they perceived ... that the field has developed rather dramatically in the last decade-and-a-half, with lots of new scientific findings, but with some evidence that neither the public nor even the relevant professional people are appreciating the full magnitude of the problem of sleep disorders," noted Dr. Colten, a pediatrician and former vice president and senior associate dean for academic affairs at Columbia University Medical Center, New York. "It happens to come at a time when research funding is tight, but we emphasize the importance of developing a sufficient workforce, too—both clinical and research workforces—to deal with this underappreciated problem."

Chock full of statistics and strategies to advance the sleep medicine field, the

report is "an important next step in the evolution of sleep medicine from its beginnings to its teenage years, and into its adulthood," said Dr. Charles W. Atwood Jr., FCCP, of the division of pulmonary, allergy, and critical care medicine at the University of Pittsburgh Medical Center. Dr. Atwood is also the Chair of the ACCP Sleep Institute.

Sleep medicine "has been growing steadily as a clinical activity, but what has not kept up with it is the realization that it's becoming a full-fledged academic activity," he observed. "Medical schools and academic medical centers really need to take notice of it and do what they can to foster the next generation of researchers who are going to make new discoveries about sleep and to train the next generation of clinicians who are going to take care of patients with sleep disorders."

Physicians can do their part, he added, by asking their patients simple questions about sleep during routine office visits. He offered the following question as an example: Do you feel like you have enough alertness to get you through the day in an adequate fashion, or are you too sleepy?

"If they seem too sleepy or if they have to fight off sleep at inappropriate times on a regular basis, that's a problem," Dr. Atwood said. The physician "should follow that up with questions about how much sleep the patient gets [and] if the patient has been told that he or she has excessive snoring or stops breathing at night. That can lead into a number of different directions. But if they ask about getting enough sleep and about potential sleep apnea, that's a good start."

The 386-page report calls for AASM accreditation of the nation's sleep disorders centers and labs for sleep-related breathing disorders. Dr. Pack estimated that only 30%-35% of the nation's sleep disorders centers and labs currently hold such credentials.

"We shouldn't really have sleep labs where you just go in and get a [sleep] test," he said.

"It's really about management of patients and improving outcomes. An important part of the accreditation procedure should be looking at the outcomes of management: How well are you doing in terms of management? There are some obvious metrics in that regard, like what your [continuous positive airway pressure] compliance data are and so on. That could be brought in to make sure that people are focusing on the outcomes and not just on the diagnosis."

Dr. Atwood considers accreditation important, "because it lends credibility to the effort that you're doing locally, and I think it provides some degree of quality assurance that you're using practices that are generally accepted as good."

The report also recommends that every academic medical center build an interdisciplinary sleep program that emphasizes long-term clinical care, training, and research.

Academic medical centers "should take a major responsibility, not only for clinical care, but they should take a major responsibility for education," Dr. Pack said. "We think it's very important that they're involved in educating primary care physicians. Primary providers need to be educated in sleep and sleep disorders: the differential,

how you recognize them, and so on."

Other key strategies in the report's executive summary include the following:

► Increase awareness of the burden of sleep loss and sleep disorders among the general public by developing a multimedia, comprehensive education campaign on the health and economic impact of sleep loss and sleep disorders.

► Establish the workforce required to meet the clinical and scientific demands of the field. In 2004, only 54 people in the United States received doctorate degrees in somnology or sleep medicine.

► Develop and validate new and existing diagnostic and therapeutic technologies. One focus "is a call for research and validation of in-home monitoring so that this bottleneck of sleep labs isn't the sole means for making a definitive diagnosis of a sleep disorder," said Dr. Colten. "That's a pressing need."

► Create a national research network that connects individual investigators, research programs, and research centers. ■

The full text of "Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem," is available online at <http://nap.edu>.

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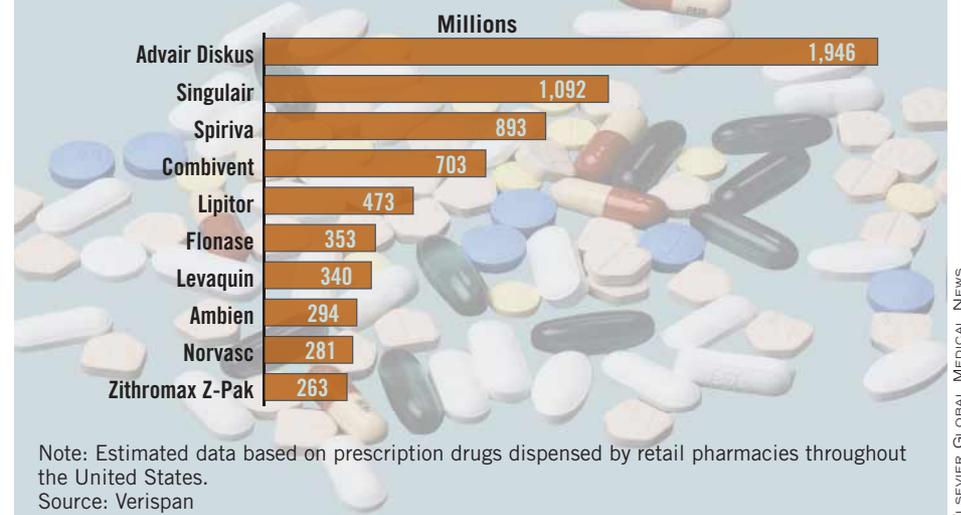
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Top 10 Drugs Prescribed by Pulmonologists in 2005



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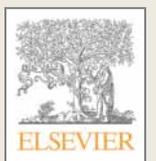
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Screening Program Reaches Out

Atlanta • from page 1

This community-based combination of education and participation is the crux of the “Not One More Life” program, and the results of the approach thus far have been very encouraging.

A Not One More Life visit to a church begins with the initial contact, logistics, and setup arranged by the program director, Melvin Butler. A team consisting of one or two physicians (usually a pulmonologist or allergist) and two or three respiratory therapists, in addition to asthma educators and other volunteers, then visits the church.

The program opens with a presentation on asthma and lung disease, with an emphasis on practical knowledge that educates attendees on what they should expect from good health care—and in particular from good asthma control.

Participants then fill out a symptom-based questionnaire drawn from the Juniper model, undergo spirometry to assess lung function, and sit down with a physician to discuss the results of the questionnaire and spirometry reading.

In contrast with a health fair, in which about half of attendees may allow themselves to undergo some type of testing, 82%-85% of participants at the Not One More Life sessions will submit to testing.

“We think that’s because of the unique trust relationship that is fostered in this setting,” Dr. Graham explained. “We are invited in and endorsed by the churches, who participate by helping set up and encouraging people to participate.”

After undergoing testing, individuals with signs of asthma or other lung disease are then provided with a report to give to their primary care providers. Those without a primary care physician, or those requiring a specialist, are referred to a network of providers. Though most participants have some insurance coverage, pro bono care is available.

“We know we’re capturing an important population, because 60% of the people who attend our sessions have either abnormal symptoms and/or abnormal lung function, while only 20% of them have

self-reported asthma,” said Dr. Graham.

The program also has revealed a disconnect in some individuals between reported symptoms and lung function test results. Between 15% and 18% of participants report no symptoms, despite having measurable abnormal lung function.

Over the past 3 years, more than 1,500 participants have attended more than 40 sessions, resulting in detection of abnormal lung function and/or symptoms in 1,200 people. Although the program was originally intended for children, it has since expanded to encompass people at all stages of life, and has served participants from age 4 to 86 years.

Unlike other programs or health fairs that have only single encounters with people, Not One More Life has a nurse outcome manager who places serial follow-up phone calls at 1, 3, and 6 months after the sessions to find out whether participants have visited a physician and are receiving treatment.

According to these follow-ups, 97% of individuals identified at the sessions as having abnormal lung function go on to visit a physician for further evaluation and treatment. This high success rate shows how effective such a comprehensive community-based program can be, the program’s leaders say.

“We’ve had some astounding success stories—people calling us up, saying, ‘I didn’t know I could feel this good!’” Dr. Graham added. In addition to asthma, Not One More Life screening has detected emphysema, sarcoidosis, chronic bronchitis, and pulmonary complications of HIV.

As the final and most expensive portion of the program, Not One More Life provides Internet-ready computers to small- and medium-sized churches. In Atlanta, only 30% of African American homes have Internet access, compared with 70% of white homes, Dr. Graham said.

By providing these computers, the program enables churches to set up a health kiosk where individuals can learn about different health topics. The program Web site, www.notonemorelife.org, contains

Organizing an Outreach Program

► **Learn about the community.** Be willing to listen and learn from the community leaders rather than having a missionary approach. A transactional approach, in which there is a partnership with the community, is much more likely to succeed, Dr. Graham said. “People don’t want to be saved—people want to be empowered,” he explained.

► **Show respect for the community.** In working with churches, realize that pastors know what works in their communities. The members of the church place their trust in pastors, and if the pastor trusts you, that trust of the people from the community will be carried over to you as well.

► **Be flexible in your scheduling.** Timing can be an important determinant of a session’s success. It is important to identify when a session would

be most beneficial. For churches, Saturday or Sunday after services often works, and can result in a spillover effect from other activities going on. In fact, some churches may have a luncheon or dinner in conjunction with the event.

► **Engage the participants.** Many participants say that they have never had a chance to sit down and talk with a doctor one on one. This individual attention can make a difference for many people.

► **Address the whole needs of the people.** In many cases, health care encompasses social and cultural issues as well. People may have a “crisis view” of health care, in which they only attend to their health when a problem arises. In these situations, it is important to explain the importance of preventative care.

information on the Not One More Life program, links to other health Web sites, and a directory of free and reduced-fee clinics.

When Not One More Life was first proposed in mid-2000, Dr. Graham and associates lacked the funds necessary to put their concept into action. So they began to pursue funding through industry sponsors. They have since received financial support from pharmaceutical companies to carry out their mission.

Until recently, these funds were distributed through a fiduciary of the American Lung Association of Georgia. However, in December 2005, Not One More Life gained nonprofit 501(c)(3) status, which allowed the program to receive contributions directly.

It is largely volunteer based, with all clinicians giving their time without compensation. Currently, the only paid individuals are the program coordinator, the nurse outcome manager, a grant writer, and a director of development.

The success of the outreach program earned Dr. Graham The CHEST Foundation’s Governor’s Community Service Award in 2004. That success may soon be

replicated beyond Not One More Life’s current settings.

Dr. Graham said he hopes to expand the reach of Not One More Life beyond asthma screening in African American churches in Atlanta. Not One More Life has visited other faith-based communities such as mosques, Southern Baptist churches, and synagogues.

Outside Atlanta, Dr. Graham has made contact with interested persons in other major U.S. cities, and he hopes to be able to spread the concept to these other areas. For those interested in starting a community-based health education and screening program, Dr. Graham has provided some perspectives based on lessons learned over the 5-year history of Not One More Life. (See box.)

Given the positive outcomes with Not One More Life, Dr. Graham believes the model could be useful in educating and screening people for a variety of disorders, including obesity, diabetes, and hypertension. Such community-based approaches may provide a real solution for addressing unmet health care needs one individual at a time, he said. ■

Medicare Reimbursement to Drop

CMS • from page 1

getting rid of the SGR—it’s always next year, next year, next year, and next year never seems to show up,” added Dr. Larry S. Fields, president of the American Academy of Family Physicians. Although legislators are unlikely to offer a permanent solution this year, the AAFP will advocate for one, he added.

“I think Congress agrees that it’s not a fair system,” Patrick Hope, legislative counsel for the American College of Physicians, said in an interview. ACP is not optimistic that the SGR will be addressed in 2006, an election year, Mr. Hope said.

Physician organizations said they will try to stop the cuts. Some also will continue to push for a system that would reward physicians with higher fees in exchange for more quality reporting, and tying physician fees to the Medicare Economic Index.

The bill introduced last year by Rep. Nancy Johnson (R-Conn.) is a good starting point for negotiations, Mr. Hope said.

The American Medical Association supported Rep. Johnson’s bill, and also will urge Congress to stop the cuts, an AMA spokeswoman said.

In a statement, Dr. Duane Cady, AMA chair, said that the 2007 reduction “is just the tip of the iceberg.” Over 9 years, the pay cuts will total 34%, while practice costs will increase 22%, Dr. Cady said. An AMA survey found that over those years, 73% of physicians will defer buying new equipment and 65% will put off purchases of new information technology—at a time when practitioners are being asked to convert to electronic health records and collect more data on quality and health outcomes.

“You can’t expect doctors to move toward electronic health records facing that kind of hit,” Mr. Hope agreed.

Dr. Fields said that physicians may stop taking new Medicare patients, or, even worse, may have to close their practices. “When the overhead is greater than the payment, there won’t be any access,” he said, adding that closures will impact private-pay patients also.

Even CMS agreed that the practice environment is getting harder. “Physicians may find it difficult to invest in activities like electronic record systems and support programs for high-risk patients that could enhance quality of care, without increasing medical costs,” Herb B. Kuhn, director of CMS’ Center for Medicare Management, wrote to the

Medicare Payment Advisory Commission.

The fastest-growing components of physician services included imaging (16% growth), laboratory and other tests (11% growth), and procedures (9% growth), according to the letter. Procedures accounted for 26% of Medicare spending, compared with 14% for imaging and 12% for laboratory and other tests.

An increase in evaluation and management services accounted for the largest portion of the 8.5% overall growth in physician services, but the growth rate—7%—was less than for the other services.

Dr. Cady said that it’s not surprising that physician services are increasing, as patients are living longer with chronic conditions and more emphasis is being placed on preventive care. ■



‘It’s always next year, next year, next year, and next year never seems to show up.’
DR. FIELDS

New Oncology Agent Up for Review for Lung Cancer

BY CHRISTINE KILGORE
Elsevier Global Medical News

The angiogenesis inhibitor bevacizumab should get a thumbs-up or -down from the Food and Drug Administration sometime this year or early next year for use in the treatment of non-squamous non-small cell lung cancer.

F. Hoffman-La Roche Ltd. and Genentech Inc., manufacturers of bevacizumab (Avastin), asked the Food and Drug Administration last month to approve the antiangiogenic agent—a monoclonal antibody—for use in combination with platinum-based chemotherapy (carboplatin plus paclitaxel) for previously untreated patients with advanced non-small cell lung cancer (NSCLC), the most common form of lung cancer.

The companies requested a “priority review” for the treatment; if granted, the agent would be reviewed within 6 months, about half the usual amount of time.

Their submission to the Food and Drug Administration is based on results of a ran-

domized, controlled phase III trial of patients with locally advanced, metastatic or recurrent NSCLC, which was presented at last year’s annual meeting of the American Society of Clinical Oncology.

At that time, presenters reported that patients receiving bevacizumab plus chemotherapy had a 30% improvement in overall survival, compared with patients who received chemotherapy alone.

According to the final analysis from Roche and Genentech, patients treated with bevacizumab plus chemotherapy had an overall median survival of 12.3 months, compared with 10.3 months for the control group.

That difference translates into a 25% improvement in overall survival.

Less than 5% of patients with advanced NSCLC survive for 5 years, and most die within 12 months.

In the United States, non-small cell lung cancer accounts for 87% of all lung cancers, according to company reports.

The drug was approved in 2004 as a front-line treatment for patients with metastatic colon cancer, based similarly on trial data showing that the drug extended patients’ lives by about 5 months when given in combination with standard chemotherapy agents.

According to the Food and Drug Administration, bevacizumab is the first product to be approved that works by preventing angiogenesis—a strategy first proposed more than 30 years ago.

It is believed to target and inhibit vascular endothelial growth factor, thus preventing the growth of blood vessels that feed tumors, the Food and Drug Administration has said.

Roche and Genentech also have been investigating the use of the drug in patients with breast cancer, as well as pancreatic, ovarian, and other cancers.

Survival improvements in patients with breast cancer were reported at the American Society of Clinical Oncology meeting last year.

Investigators also reported at that meeting improvements in patients with non-small cell lung cancer and colorectal cancer.

In the pivotal trial on which the Food

and Drug Administration application for use in NSCLC is based, patients received bevacizumab at a dose of 15 mg/kg every 3 weeks, plus paclitaxel and carboplatin.

In addition to improvements in overall survival among patients who received bevacizumab plus chemotherapy, the study also showed a 54% improvement in progression-free survival.

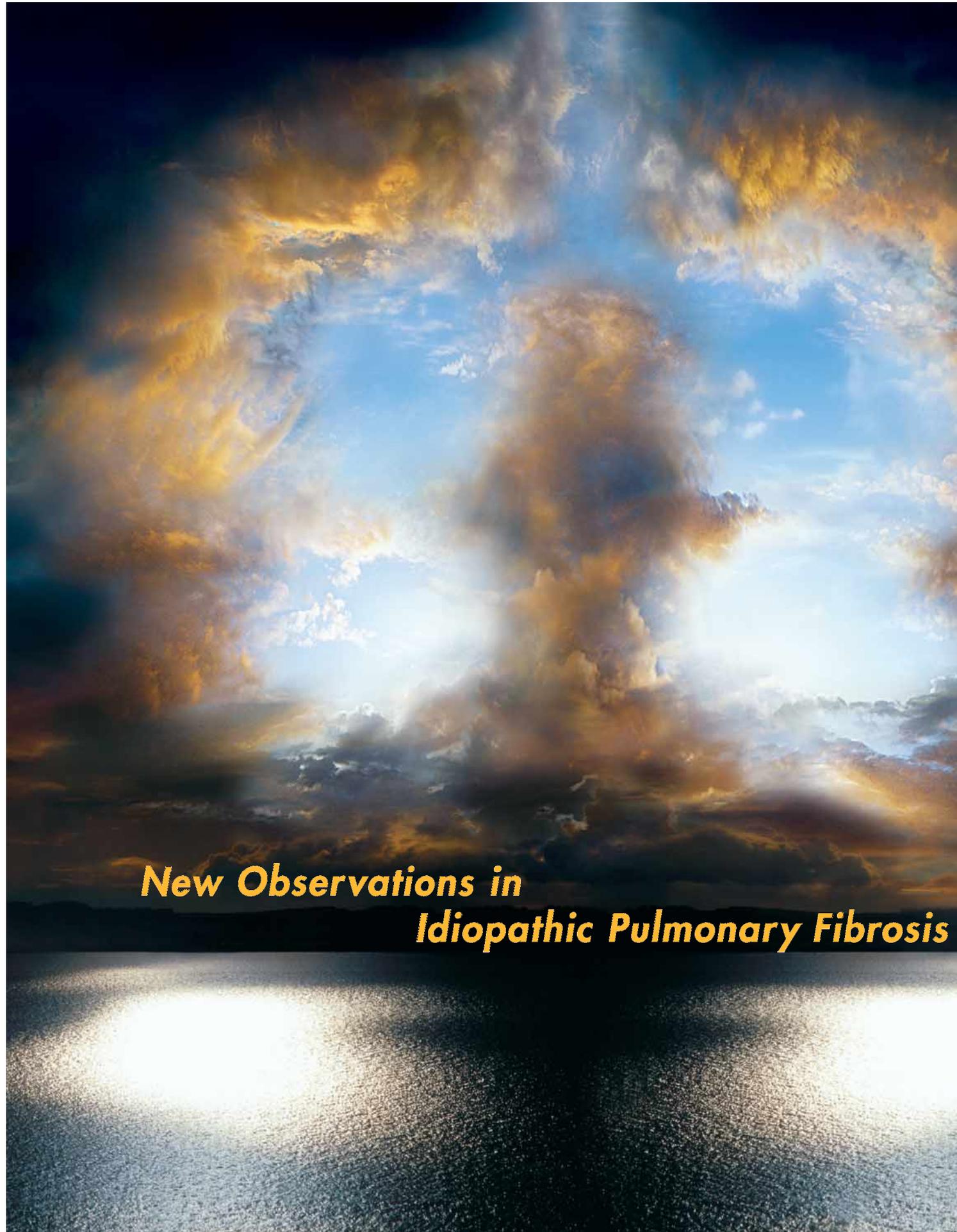
The bevacizumab group also demonstrated a higher response rate, compared with chemotherapy alone (29% vs. 13%).

Pulmonary hemorrhage was observed in 2.3% of the patients who were receiving bevacizumab plus chemotherapy.

At the American Society of Clinical Oncology meeting last year, a lead investigator reported that the overall survival benefit from treatment with bevacizumab occurred in every subgroup except women.

Women still benefited, however, from the bevacizumab treatment effects in terms of progression-free survival and response, the investigators reported. ■

NSCLC PATIENTS RECEIVING BEVACIZUMAB PLUS CHEMOTHERAPY HAD A 30% IMPROVEMENT IN OVERALL SURVIVAL.



New Observations in Idiopathic Pulmonary Fibrosis

Late-Onset Anaphylaxis to Omalizumab Reported

BY PATRICE WENDLING
Elsevier Global Medical News

MIAMI BEACH — Two patients developed anaphylaxis to the popular allergic asthma medication omalizumab after months of successful treatment, Dr. Kursteen Price reported in a poster at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

This is the first report of late-onset anaphylaxis to the humanized monoclonal anti-immunoglobulin E (IgE) antibody

omalizumab (Xolair), Dr. Price said.

According to the prescribing information for omalizumab, “anaphylaxis has occurred within 2 hours of the first or subsequent administration of Xolair in 3 [less than 0.1%] patients without other identifiable allergic triggers.”

“We can’t get too nonchalant about it,” Dr. Price said in an interview. “There is still the potential that patients can develop a bad reaction to the medicine. We need to look at it with caution, but I think that it’s still a very useful medication.”

According to theory, anaphylaxis to omalizumab would not occur if the drug were working. That is because omalizumab decreases IgE, which is needed to stimulate the release of histamine and other mediators during anaphylaxis.

But a second mechanism has been described in mouse models in which anaphylaxis occurs through IgG mediation, said Dr. Price, an allergist in private practice in Portland, Ore. One of the patients who developed an anaphylactic reaction also was sensitive to polysorbate in eye drops, and

polysorbate is present in omalizumab.

She reported on a 56-year-old woman with previously steroid-dependent asthma who developed itching and redness at the injection sites within 5 minutes of receiving her 27th bimonthly treatment with omalizumab 150 mg. Rapidly generalized itching, chest tightness, and a sense of impending doom were described by the patient, who was determined to be hypotensive and tachycardic.

The patient was given intramuscular and subcutaneous epinephrine, oxygen, a bolus of 500 mL of saline, 10 mg each of cetirizine and montelukast, and methylprednisolone (Solu-Medrol) 40 mg intramuscularly. She recovered hemodynamically within 15 minutes and was discharged hours later with no further sequelae.

One month after this anaphylactic episode, intradermal testing to omalizumab at a dilution of 1:1,000 showed a significant wheal-and-flare reaction of 10 mm/10 mm in the patient, who became symptomatic and required oral antihistamine for generalized itching.

The second case was quite different, and occurred within minutes of the 13th treatment in a woman with asthma and reflux receiving monthly treatments. There was no local injection site reaction,

ONE OF THE PATIENTS WHO DEVELOPED ANAPHYLAXIS ALSO WAS SENSITIVE TO POLYSORBATE IN EYE DROPS, AND POLYSORBATE IS PRESENT IN OMALIZUMAB.

but the patient developed asthma, acute hives, and tightness in her throat that peaked 4 days after omalizumab therapy. She was hospitalized on the fifth day, treated, and released 2 days later. Her respiratory symptoms persisted for a month, and she required repeated treatments with epinephrine and steroids, Dr. Price said. The patient did not skin-test positive.

Novartis Pharmaceuticals, which jointly markets omalizumab with Genentech, would not confirm whether these are the first or only cases of late-onset anaphylaxis. Any spontaneous reports received in the postmarketing setting are reviewed and submitted to the Food and Drug Administration, Megan Humphrey, Novartis director of communications, said in an interview.

“The reason these patients are on Xolair is because they’re uncontrolled with other medications and continue to have allergic reactions,” she said. “There’s just no way to tell when such a person might have an allergic reaction.” In the United States, there have been more than 25,000 prescriptions for omalizumab since it was launched in June 2003, Ms. Humphrey said. ■

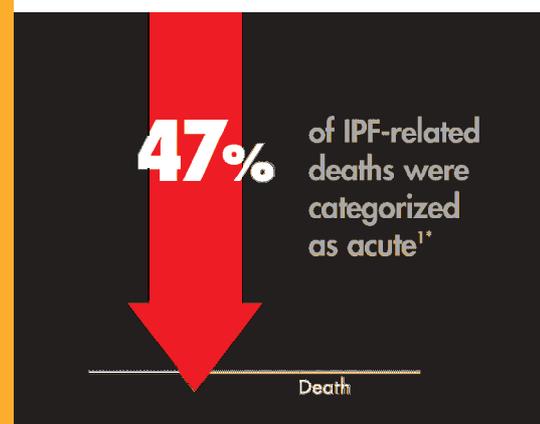
Dr. Susan M. Harding, FCCP, comments: Clinicians beware! Late-onset anaphylaxis with omalizumab is possible, even months after initiating therapy—rare, but possible. Schedule these injections early during your office time so that your patients are adequately observed and appropriate therapy is immediately available.

#2 in a series

The Nature of IPF: Rapid Fatal Deterioration

Data show that the clinical course of IPF often involves acute (≤ 4 weeks) fatal deterioration, even in patients with only mild to moderate disease.^{1*}

The risk of acute fatal deterioration^{1*}



*Data from a retrospective analysis of 168 patients with mild to moderate IPF in the placebo arm of a phase 3 trial. Most (89%) of the deaths that occurred were due to IPF-related causes. Nearly half (47%) of these deaths were preceded by a period of deterioration lasting ≤ 4 weeks.

The insidious nature of IPF and the risk of rapid fatal deterioration may make early referral to a randomized clinical trial or for lung transplantation a good option in patients diagnosed with the disease.¹⁻⁴

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(IPF)

Inhaled AMP May Help Differentiate COPD, Asthma

It also holds promise for monitoring airway inflammation and response to treatment.

BY PATRICE WENDLING
Elsevier Global Medical News

MIAMI BEACH — Measuring airway responsiveness to inhaled adenosine helps discriminate between a diagnosis of asthma and chronic obstructive pulmonary disease.

It's also a valuable clinical tool for monitoring airway inflammation and response to anti-inflammatory treatment in asthma, Dr. Riccardo Polosa reported at the annual meeting of the American Academy of Allergy, Asthma, and Immunology. "AMP challenge is noninvasive, non-time consuming, low cost, has good reproducibility and patient acceptability, and safety is optimal," he said.

Adenosine 5'-monophosphate (AMP) is a proinflammatory mediator that induces bronchoconstriction in patients with inflammatory lung diseases. Response to AMP is determined by measuring the concentration of inhaled AMP causing the forced expiratory volume in 1 second (FEV₁) to decrease by 20%. The exact cutoff point between normal and abnormal PC20 AMP, as it is known, remains

somewhat unclear. But a cutoff of 160 mg/mL has been used successfully to discriminate between asthmatics and healthy controls. AAAAI is considering standardizing and writing protocols for AMP and other indirect challenges, said session moderator Dr. Richard A. Nicklas of George Washington University, Washington, D.C.

Dr. Polosa and his colleagues at the University of Catania (Italy) have shown that airway responsiveness to inhaled AMP is closely related to the number of eosinophils in the airways of atopic patients, whereas no association was observed with methacholine, one of the most commonly used agents for assessing bronchial hyperresponsiveness (Eur. Respir. J. 2000;15:30-5).

Dr. Polosa and other researchers from the university also showed that PC20 AMP could detect inflammatory changes as early as the first week of treatment with inhaled budesonide 0.8 mg per day in mild to moderate asthmatics, while methacholine responsiveness and changes in the percentage of sputum eosinophils could be observed only by the fourth week of treatment (J. Allergy Clin. Immunol. 2002;110:855-61).

Investigators at King's College, London, were able to demonstrate in three consecutive studies that a single dose of intranasal fluticasone propionate 100-1,000 mcg inhibited an asthmatic response to AMP in just 2 hours in patients with mild, stable asthma. A single inhalation of fluticasone 1,000 mcg had no effect on airway responsiveness to histamine (J. Allergy Clin. Immunol. 2002;110:603-6).

But when Dr. Polosa's team performed a similarly designed randomized, double-blind study using a single inhalation of fluticasone 1,000 mcg in 14 patients with chronic obstructive pulmonary disease (COPD) and 13 with mild asthma, there was a change in response in only one of the COPD patients, he said. The experiment was repeated with similar results in 10 patients with a clear history of asthma and 10 patients with COPD and comparable fixed airway obstruction.

"This tells me very nicely that AMP challenge can be used as a strong discriminator for COPD and asthma," he said of the unpublished findings.

AMP also has been used to assess the nonsteroidal anti-inflammatory potential of several therapeutic agents including allergen immunotherapy (Clin. Exp. Allergy 2003;33:873-81), the leukotriene receptor antagonist montelukast (Am. J. Respir. Crit. Care Med. 2003;167:1232-8), and the humanized monoclonal anti-IgE antibody

omalizumab (Int. Arch. Allergy Immunol. 2006;139:122-31).

AMP may be a more useful and sensitive diagnostic tool than challenging patients with methacholine and histamine because of its unique mechanism of action, Dr. Polosa said. Histamine and methacholine have a direct spasmogenic effect on airway smooth muscle cells. AMP acts indirectly via the secondary release of mediators. ■

Dr. Mark Dransfield comments: *These initial results are interesting, as at present there is no bronchodilator or bronchoprovocation test that can be used to differentiate asthma and COPD. That said, larger studies are needed to confirm the findings and to standardize AMP dosing. Clinicians should be mindful that AMP challenge is not currently approved by the FDA.*

COPD Info for Seniors

Seniors can now find information about the diagnosis and treatment of chronic obstructive pulmonary disease (COPD) on the NIH Senior Health Web site. The site provides information about the causes and symptoms of and existing treatments for the disease. Visit <http://nihseniorhealth.gov/copd/toc.html>.

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Fatal Asthma Shifting to the Elderly, Declining Overall

BY PATRICE WENDLING
Elsevier Global Medical News

MIAMI BEACH — Preliminary data from a fatal asthma registry suggest that asthma deaths continue to decline and are more common in the elderly, Dr. Carlos Camargo Jr., FCCP, said at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

Dr. Camargo and colleagues at Massachusetts General Hospital, Boston, developed a standard protocol for contacting next of kin that was submitted to institutional review boards in four states: Arkansas, Missouri, Ohio, and Massachusetts. So far they have identified 222 possible asthma fatalities, a number that is significantly lower than would have been predicted in the late 1990s when asthma rates were climbing, he said. Estimates vary, but 5,500 asthma deaths occurred annually in the early 1990s compared with about 4,300 today.

An analysis of the first 20 deaths in Massachusetts showed that half of deaths occurred in patients older than 80 years. In almost two-thirds of the 20 fatalities, families reported that the patient who died had a history of anxiety or depression in the previous 12 months.

Most of the 20 deaths occurred in the hospital, and almost half of the deaths occurred in patients who had visited an emergency department in the previous 12 months.

"This is a different picture of asthma mortality than is generally believed," said Dr. Camargo, chair of the academy's asthma mortality committee.

"There have been some reports in recent years on how deaths are occurring more in the elderly, but I think it's getting more dramatic," he said.

The most common triggers of death were allergens or cold weather. Nearly three-fourths of the 20 patients who died had reported frequent night awakening due to their asthma prior to their deaths, consistent with a more persistent affliction. The study was funded by an unrestricted grant from GlaxoSmithKline.

The finding that many asthma deaths are occurring in the elderly has sparked efforts to create the Veterans Affairs Fatal Asthma Project, which will match cases of asthma deaths with age-matched controls living with asthma, and which aims to evaluate their health care utilization. Veterans Affairs centers in Ohio, Wisconsin, Massachusetts, and Arizona are enrolled, but Dr. Camargo urged audience members who work in the VA to contact him to broaden participation.

All of these efforts to create a national fatal asthma registry have been hampered by the Health Insurance Portability and Accountability Act and different internal review board interpretations that preclude a standardized national approach for contacting next of kin, he said (J. Asthma 2006;43:19-23). ■

Diabetes Risk Elevated With Smoking, Secondhand Smoke

BY MELINDA TANZOLA
Elsevier Global Medical News

Both smoking and exposure to secondhand smoke increase the risk of developing glucose intolerance, results of a prospective cohort study indicate.

Over the 15-year study period, the development of glucose intolerance was highest among smokers (22%), followed by people who had never smoked but had secondhand smoke exposure (17%), previous smokers (14%), and those who neither smoked nor had secondhand smoke exposure (11.5%).

The investigators noted that this was the first study to demonstrate that secondhand smoke is independently associated with a risk of developing glucose intolerance (BMJ 2006 April 7 [Epub doi.10.1136/bmj.38779.584028.55]).

In the Coronary Artery Risk Development in Young Adults (CARDIA) study, Dr. Thomas K. Houston of the Birmingham (Ala.) Veterans Affairs Medical Center and his associates enrolled young adults, aged 18-30, from four U.S. cities.

The cohort included 1,386 smokers, 621 previous smokers, and 2,565 individuals who had never smoked; all had normal glucose tolerance levels at baseline. The "never smokers"

included 1,452 people with secondhand smoke exposure, which was validated by a serum cotinine concentration of between 1 and 15 ng/mL.

Study participants received thorough examinations at baseline and at years 2, 5, 7, 10, and 15 that assessed medical and sociodemographic information, including economic, psychosocial, and nutritional parameters. They also were interviewed via telephone each year. By year 15, 26% of the original cohort was lost to follow-up.

After 15 years, 17% of the study population had developed glucose intolerance, which was defined as having either impaired fasting serum glucose levels—with levels greater than or equal to 100 mg/dL and less than 126 mg/dL—or diabetes, with serum glucose levels greater than or equal to 126 mg/dL.

Compared with people who had never smoked and weren't exposed to secondhand smoke, current smokers (hazard ratio of 1.65), never smokers with secondhand smoke exposure (hazard ratio of 1.35), and previous smokers (hazard ratio of 1.17) remained at increased risk for developing glucose intolerance, after adjusting for confounding variables.

Each 10-pack-year increase in smoking increased the risk of developing glucose intolerance by 18%. ■

Pneumonia Mortality Cut by Vaccination

BY MELINDA TANZOLA
Elsevier Global Medical News

Prior pneumococcal vaccination significantly improves outcomes in adults hospitalized with community-acquired pneumonia, results of a recent retrospective study suggest.

Compared with unvaccinated adults, those who had received the pneumococcal vaccine were 50% less likely to die while in the hospital and 33% less likely to develop respiratory failure, after adjustment for confounding factors (Clin. Infect. Dis. 2006;42:1093-101).

"Whether or not [the vaccine] prevents pneumonia is almost irrelevant—it clearly has an effect on reducing death in the individuals who get pneumonia," Dr. David N. Fisman, lead study author, said in a statement released by the Infectious Diseases Society of America.

Dr. Fisman of Drexel University

in Philadelphia and his associates evaluated the benefits of prior pneumococcal vaccination in 62,918 consecutive adult patients hospitalized with community-acquired pneumonia at 109 hospitals.

In addition to the reductions in death or respiratory failure, vaccination also significantly reduced the in-hospital risk of acute respiratory distress syndrome, sepsis syndrome, cardiac arrest, and acute renal failure. Vaccinated individuals spent a median of 2 fewer days in the hospital.

Twelve percent of the cohort had received the vaccination, 23% were unvaccinated, and the vaccination status was unknown for the remaining 65% of the patients.

The Centers for Disease Control and Prevention aims to increase the vaccination rate to 90% of older adults by 2010; the pneumococcal vaccine is recommended for persons aged 65 years and older and for younger persons with certain medical problems. ■

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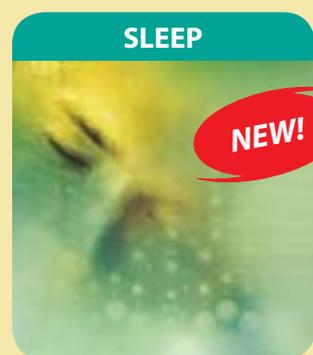
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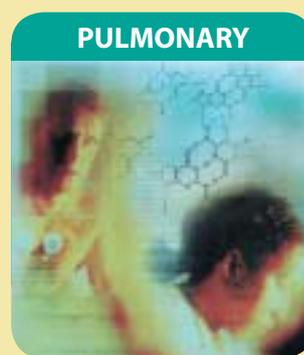
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Adenotonsillectomy Linked to Improved ADHD

BY ROBERT FINN

Elsevier Global Medical News

Half of all children undergoing adenotonsillectomy who were found to have attention-deficit hyperactivity disorder before the surgery no longer met the diagnostic criteria a year later, according to a prospective, controlled study.

The study strengthens previous observations that linked sleep-disordered breathing—a major reason for adenotonsillectomy—with attention and behavior problems.

The investigators, led by Dr. Ronald D. Chervin of the University of Michigan, Ann Arbor, acknowledged that their study does not prove cause and effect. And they also acknowledged that their study leaves an important puzzle: Although they found a strong link between adenotonsillectomy and neurobehavioral improvements (behavior, cognition, and sleepiness), they also found that sleep-disordered breathing at baseline and its subsequent improve-

children was 7.3 events per hour, compared with 1.2 events per hour for the control children.

A year later, there were no significant differences between the adenotonsillectomy children and the control children on any polysomnographic measure. The average AHI of the control children remained 1.2 events per hour, while that of the adenotonsillectomy children declined to 1.1 per hour.

Twenty-two (28%) of the adenotonsillectomy children had ADHD at baseline,

compared with only two (7%) of the control children, a significant difference. Eleven of those 22 children no longer qualified for the diagnosis a year later, and there was no significant difference between the frequencies of ADHD in the two groups.

However, there was no significant association between measures of sleep-disordered breathing and either baseline or follow-up neurobehavioral morbidity. The lack of an association could reflect inadequate sample size, the researchers said, but they noted that the sample size was more

than sufficient to identify statistically significant postoperative changes in several other variables.

Another possibility is that standard measures of sleep-disordered breathing may not adequately assess the mild form of this condition that is common among children referred for adenotonsillectomy.

There is also the possibility that some correlate of sleep-disordered breathing, rather than sleep-disordered breathing itself, is the true cause of the neurobehavioral morbidity. ■

THE STUDY STRENGTHENS PREVIOUS OBSERVATIONS THAT LINKED SLEEP-DISORDERED BREATHING WITH ATTENTION AND BEHAVIOR PROBLEMS.

ment did not predict either baseline neurobehavioral morbidity or its improvement in any area aside from sleepiness (Pediatrics 2006;117:e769-78).

The study involved 78 children between 5 and 13 years of age who were scheduled for adenotonsillectomy for any indication. They were compared with 27 control subjects in the same age range who were recruited from other surgical clinics. Among the children receiving adenotonsillectomy, 71 (91%) were judged to have a nocturnal upper airway obstruction.

Children were excluded from the study group if they required a polysomnogram for clinical purposes, if they had a history of treatment for sleep-disordered breathing, or if they had severe medical or neurologic conditions. Children were excluded from the control group for those reasons and also if they had a history of large tonsils, frequent throat infections, adenoidectomy, or tonsillectomy.

At baseline—generally within 1 month before scheduled surgery—all children underwent full-night polysomnography, and the next day received a battery of neurobehavioral assessments including the multiple sleep latency test of daytime sleepiness and a number of neuropsychological tests. Polysomnography and neurobehavioral assessments were repeated at follow-up, about 1 year later.

Before surgery, children scheduled to undergo adenotonsillectomy were significantly worse than the control children on several measures of sleep-disordered breathing, including minimum oxygen saturation (an index of obstructive apnea), a respiratory disturbance index, and the apnea-hypopnea index (AHI). For example, the average AHI of the adenotonsillectomy

CRITICAL INSIGHTS INTO THE NATURE OF NICOTINE ADDICTION

A SUMMARY OF KEY LEARNINGS TO DATE

With all the public awareness efforts that have been made, and with all the truths that have come to light over the last several decades about the dangers of smoking, one obvious question lingers: **Why are people still smoking?**

Understanding nicotine addiction

Most experts agree at this point that smoking is a chronic, relapsing condition—an addiction similar in nature to that seen in cocaine and heroin users.^{1,2} Following are 4 criteria the Surgeon General has used to define addiction, along with an explanation of how nicotine—specifically smoking—meets these criteria.²

1. Addiction leads to compulsive use, despite adverse consequences

According to a 1988 Surgeon General's report, "highly controlled or compulsive use indicates that drug-seeking and drug-taking behavior is driven by strong, often irresistible urges. It can persist despite a desire to quit or even repeated attempts to quit."² Smoking statistics show that approximately **70% of current smokers report that they want to quit**; however, only about 5% of smokers who try to quit without medical aid succeed.^{3,4} In fact, the average smoker has tried to quit **6 to 9 times**.⁵ It is common for people to continue smoking despite known negative health consequences. In fact, smoking behavior often persists even after the presentation of comorbid conditions.^{2,6,7}

2. Addiction involves a psychoactive substance with reinforcing properties

The psychoactive (mood-altering) properties of nicotine are substantially related to its effect on the mesolimbic dopaminergic system. For delivery of nicotine, smoking is the most efficient mechanism. In a matter of seconds, nicotine from inhaled smoke crosses the blood-brain barrier and begins altering brain chemistry through binding to

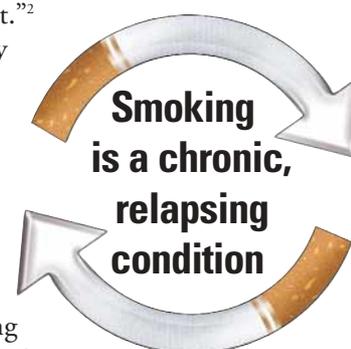
cholinergic receptors normally activated by acetylcholine. Dopamine is released in the nucleus accumbens, triggering central nervous system effects such as pleasure, relief of anxiety, better task performance, and improved memory. These rewards serve to reinforce smoking behavior.^{2,8-10}

Complicating this effect is that the routines associated with smoking, such as smoking in social environments, can also come to be reinforced through the pleasure response. Eventually, the pleasure associated with smoking in these settings acts as a subconscious trigger, making it hard for the smoker to dissociate the behavior from the addiction. **This explains why successful quit attempts often require some degree of behavioral modification.**^{2,11,12}

3. The addicted subject develops tolerance

Nicotine initiates its action by competitively binding at the nicotinic acetylcholine receptors (nAChRs), ligand-gated ion channels on the cell membrane. Compared with the endogenous agonist acetylcholine, nicotine causes a prolonged activation of nAChRs. The activation is followed by a desensitized state in which the receptors are unresponsive to agonists. This process has been compared to tripping a circuit breaker.^{10,11,13}

Chronic use of nicotine leads to chronic desensitization of nAChRs. As more nicotine is consumed, and more receptors become desensitized, **the user experiences a diminished pleasure effect with each subsequent cigarette smoked**. As the response decreases, increasing levels of nicotine are required to achieve a consistent, desired effect.^{2,10-12} These are defining characteristics of tolerance.¹⁴



Mask Ventilation Failure: Know the Predictors

BY BRUCE K. DIXON
Elsevier Global Medical News

Whiskers, when combined with certain other patient characteristics, impede proper airway management in the surgical suite, according to a study of over 22,000 mask ventilation attempts at the University of Michigan in Ann Arbor.

"If a bearded patient is overweight, has a history of snoring, and can't pass the jaw protrusion test, mask ventilation may be

difficult or impossible and he should be asked to shave," Dr. Sachin Kheterpal said in an interview.

The investigators launched the 2-year study using a 5-point scale to grade mask ventilation (MV) difficulty. "We used a prospective, observational study to identify cases of grade 3 MV (inadequate unstable ventilation, or requiring two providers to maintain saturation), grade 4 MV (impossible to ventilate), and difficult intubation," they said. Grade 1 MV signifies no difficulty, whereas a grade 2

situation is not as easy and may require the use of an oral or nasal airway, Dr. Kheterpal explained.

Of the 22,660 cases in which mask ventilation was attempted, there were 313 episodes of grade 3 mask ventilation (1.4% of MV attempts) in adult patients, and 37 episodes (0.16%) of grade 4 MV, he said. In the grade 4 mask ventilation episodes, Dr. Kheterpal said they could not ventilate despite using an oral airway and having two providers present. "Despite all the tricks of the trade at our

disposal, we still could not move air in and out of that patient without using a tube or laryngeal mask airway," he said. There were 84 cases (0.37%) of grades 3 or 4 MV with difficult intubation.

Statistical analysis revealed that the independent predictors of difficult MV included having a body mass index (kg/m^2) of 30 or greater; having a beard, exhibiting a Mallampati class III or IV pharynx on airway examination, being older than 57 years; having a history of snoring; and being unable to protrude the jaw forward. Independent predictors of grade 4 MV included snoring and a hyoid-to-mentum distance shorter than 6 cm.

"The jaw protrusion test is one that historically has been recommended by the American Society of Anesthesiologists. In the past we have not used this test at the University of Michigan and little data

4. An addictive substance causes physical dependence, as evidenced by withdrawal and relapse

The symptoms of nicotine withdrawal have been clearly identified and confirmed. For most smokers, these symptoms include at least one, if not several, of the following: craving, irritability, insomnia, headache, anxiety, depression, and impaired concentration.^{11,14} These withdrawal symptoms have been identified as key contributors to relapse, as the smoker often "self-medicates" with nicotine to return to a perceived state of normalcy.¹²

Additionally, chronic stimulation at the receptor site is believed to be responsible for upregulation (an increase) in the number of receptors expressed at the cell surface.^{8,10,12} This is likely a result of the brain compensating for the desensitization of existing receptors, as described earlier.

As nicotine leaves the system, however, desensitized receptors can return to an "open" state in which they are once again susceptible to stimulation.^{10,11} The combination of these factors—ie, a greater number of available, sensitized receptors—may create "an excess excitability of the nicotinic cholinergic systems of smokers."¹² This hyperexcitable state is believed to contribute to the smoker's motivation to smoke another cigarette (craving).^{9,12}

Hyperexcitability may also explain why the first cigarette smoked following a period of abstinence provides a more intense pleasure response for the smoker.^{11,12} Note, for example, that most smokers derive the greatest pleasure from their first cigarette of the day.^{10,12} **In fact, smoking a single cigarette following a cessation attempt often prompts a complete relapse to heavy smoking.**^{10,11}

'IF A BEARDED PATIENT IS OVERWEIGHT, HAS A HISTORY OF SNORING, AND CAN'T PASS THE JAW PROTRUSION TEST, MASK VENTILATION MAY BE DIFFICULT.'

were available on its utility, other than the original studies," said Dr. Kheterpal. The test involves jutting out the jaw so that the lower teeth protrude beyond the upper teeth, enabling the patient to bite his upper lip.

Only one other study in the literature has examined risk factors for difficult mask ventilation (DMV), Dr. Kheterpal said. In that study of 1,502 patients, investigators found that, in a general adult population, the reported incidence of difficult mask ventilation was 5%. DMV was reported more frequently when intubation was difficult and when anesthesiologists did not accurately predict difficult mask ventilation during the preoperative visit. Five criteria—age older than 55 years, BMI greater than 26, lack of teeth, presence of a beard, snoring history—were independent risk factors for DMV (*Anesthesiology* 2000; 92:1229-36).

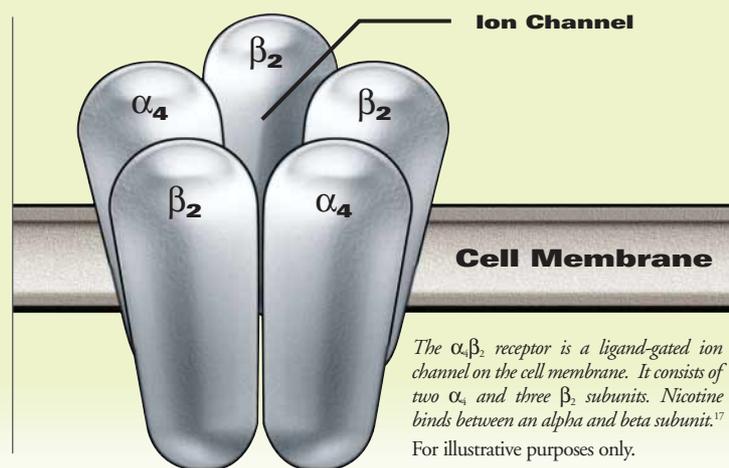
"We believed that more research is needed to be done to confirm that study's results and to look at previously unstudied parameters, such as the jaw protrusion test," Dr. Kheterpal said in an interview.

In any given practice, "about 1 in 50 patients coming to the [operating room] is going to be impossible to ventilate," said Dr. Kevin K. Tremper, professor and chair of anesthesiology at the University of Michigan and a coauthor of the study. He added that most patients in that situation can still be intubated: "In our study population, there was only one person in whom we could do neither and had to do a tracheostomy."

The bottom line, according to Dr. Tremper: "If a surgery patient is obese, snores, can't protrude his jaw, and happens to have a beard, he should be informed that he's at risk of a rare but serious problem and therefore should seriously consider shaving off the beard." ■

The $\alpha_4\beta_2$ receptor

Recent evidence suggests that scientists have identified a specific nAChR in the brain that is believed to act as a primary mediator of the addictive properties of nicotine—the $\alpha_4\beta_2$ receptor.¹⁵⁻¹⁷ The isolation and characterization of this receptor is a significant advancement in the understanding of the neurobiology of smoking addiction.



Conclusion

Smoking is a chronic, relapsing condition. For most smokers, the compounding effects of behavioral, psychological, and physical triggers make overcoming their addiction extremely difficult. However, given the high morbidity and mortality related to smoking,^{3,8} getting smokers to quit is important. Proactive medical intervention for smokers may be beneficial.¹ Recent advancements in the study of nAChRs—specifically the identification and characterization of the $\alpha_4\beta_2$ receptor—represent a significant advancement in the understanding of the nature of nicotine addiction.

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Adenotonsillectomy Improved Kids' Obstructive Sleep Apnea

BY ROBERT FINN
Elsevier Global Medical News

RANCHO MIRAGE, CALIF. — Children who undergo adenotonsillectomy for severe obstructive sleep apnea show significant decreases in heart rate and heart-rate variability, according to a poster presented at a conference on sleep disorders in infancy and childhood sponsored by the Annenberg Center for Health Sciences.

"Resolution of tachycardia and diminished pulse-rate variability after treatment of severe obstructive sleep apnea syndrome illustrates the stress that recurrent airway obstruction during sleep places on the cardiovascular system," said Dr. Evelyn Constant and colleagues from Montreal Children's Hospital.

They also speculated that pulse rate and pulse-rate variability, as measured by pulse oximetry, may be useful in diagnosing obstructive sleep apnea syndrome (OSAS), especially in those children who do not show oxygen desaturation.

The study involved 26 children, aged 1-18 years, who were referred for

adenotonsillectomy after exhibiting McGill oximetry scores of 3 or 4, indicating moderate or severe OSAS. The investigators excluded children who had congenital or genetic conditions; those with cardiorespiratory, neurological, or neuromuscular conditions; and those with global developmental delay.

Postop home oximetries and parental questionnaires were completed in the months after the surgery. The average age of the children at surgery was 4.4 years, and at postop oximetry it was 4.8 years.

The surgery resulted in significant improvement in several measures of oxygen saturation. For example, the mean minimum saturation increased from 67% to 87%, and the number of falls in saturation at or below 90% decreased from 5.3 per hour to 0.2 per hour.

Following adenotonsillectomy, pulse rate decreased significantly in 21 of the patients (81%), and pulse-rate variability decreased significantly in 23 (88%). The mean pulse rate declined from 101 beats per minute (bpm) to 91 bpm, and the standard deviation of the pulse rate declined from 10 bpm to 8 bpm. ■

CPAP May Counter Sleep Apnea's Cardiac Effects

BY MELINDA TANZOLA
Elsevier Global Medical News

People with severe obstructive sleep apnea have structural and functional cardiac changes, but these abnormalities may improve after treatment with a continuous positive airway pressure device, results of a recent study suggest.

"The implications of this study are profound, indicating OSA [obstructive sleep apnea] as a new primary cause of hypertension," wrote study investigator Dr. Bharati Shivalkar of the University Hospital Antwerp (Belgium) and associates.

The researchers found right ventricular dilatation, left ventricular hypertrophy, and reduced function of both ventricles in 43 patients with severe OSA and significant daytime sleepiness. Mean apnea-hypopnea index (AHI), which indicates the number of episodes of hypopnea and apnea per hour of sleep, was 42. The patients had a mean body mass index of 31.6, indicating obesity. Six months after receiving CPAP treatment, individuals had significant improvements in apnea symptoms, hemodynamics, and ventricular morphology and function (*J. Am. Coll. Cardiol.* 2006;47:1433-9).

At baseline, patients with obstructive sleep apnea had a significantly higher mean resting blood pressure, compared with 40 age-matched, overweight controls (153/88 mm Hg vs. 132/78 mm Hg). Their mean

resting heart rate was also significantly higher, at 77 vs. 68 beats per minute (bpm). Compared with controls, individuals with apnea had dilated right ventricles and thicker interventricular septa.

A total of 25 of the 43 patients were evaluated after 6 months of CPAP treatment. Several functional measures were significantly improved in these patients, including left ventricular ejection fraction and stroke volume, tissue Doppler-determined systolic and diastolic velocities for the left and right heart, and right and left ventricular performance. Blood pressure dropped significantly from 159/92 mm Hg to 138/80 mm Hg after treatment. Heart rates declined significantly from 73 bpm to 67 bpm.

Multiple morphologic and functional cardiac measurements correlated significantly with AHI scores. The investigators identified three parameters—interventricular septum thickness, right ventricular free wall, and mitral annulus tissue Doppler systolic velocities—that significantly predicted a higher AHI score. ■

Dr. Susan M. Harding, FCCP, comments: Although only 58% of subjects had 6-month follow-up, these data support the notion that 6 months of CPAP therapy improves blood pressure, heart rate, and left ventricular ejection fraction. The time is right to design and perform a multicenter trial examining cardiovascular outcomes with CPAP therapy.

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- Positive Airway Pressure Treatment for Obstructive Sleep Apnea: Beyond the Basics
Neil S. Freedman, MD, FCCP

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Acetazolamide Improved HF-Related Central Apnea

BY MELINDA TANZOLA
Elsevier Global Medical News

A 6-day course of acetazolamide appeared to improve sleep-disordered breathing in a study of 12 men with heart failure-related central sleep apnea.

In central sleep apnea (CSA), respiration temporarily ceases because of a decline in partial pressure of carbon dioxide (PCO₂) below the apneic threshold. However, in a study by Dr. Shahrokh Javaheri, FCCP, and his associates, the diuretic and respiratory stimulant acetazolamide seemed to reduce the likelihood of PCO₂ crossing the apneic threshold by inducing a state of metabolic acidosis.

"Although acetazolamide has been used in congestive heart failure for many years, there are no systematic studies regarding its effect on Cheyne-Stokes breathing," said Dr. Javaheri of the University of Cincinnati.

In a randomized, double-blind, placebo-controlled study, Dr. Javaheri and associates evaluated acetazolamide in 12 male patients with stable heart failure with left ventricular systolic dysfunction and demonstrated CSA (*Am. J. Respir. Crit. Care Med.* 2006;173:234-7).

For 6 nights, patients received either placebo or a single-dose (3.5 mg/kg) of acetazolamide and 30 mEq of potassium

chloride (to offset the urinary potassium loss caused by acetazolamide) 1 hour before their bedtimes. The acetazolamide dosage was increased to 4.0 mg/kg on the third day, to achieve a total CO₂ decrease of 5 mmol/L. After a 2-week washout period, crossover studies were initiated.

The mean baseline frequency of central apnea was 44 episodes per hour. When patients were treated with acetazolamide, CSA frequency was 23 episodes/hour, compared with 49 episodes/hour when they received placebo. Arterial oxyhemoglobin saturation also improved significantly with acetazolamide, although other sleep-related and pulmonary measurements were similar between study arms.

Acetazolamide caused mild metabolic acidosis in the morning. One patient on the study who was on the cardiac transplantation list developed shortness of breath while on acetazolamide. No instances of paresthesias were noted.

Patients reported significant improvements in sleep quality, daytime fatigue, and other symptoms with acetazolamide.

"In spite of the short duration of the study and modest reduction in periodic breathing, patient perception improved," the investigators noted. They hypothesized that long-term improvement in periodic breathing could, in turn, improve cardiac function. ■

Pulmonary Perspectives

Safety of Long-Acting Beta-Agonists: As Simple as Black or White?

The recently published Salmeterol Multicenter Asthma Research Trial (SMART) has prompted renewed discussion regarding the safety of long-acting beta-agonist (LABA)-containing medications as part of daily asthma therapy (Nelson et al. *Chest* 2006; 129:15).

The 28-week placebo-controlled study of salmeterol added to "usual" asthma care revealed, among other findings, significant increases in treatment group asthma-related deaths in the study population of 26,355 subjects.

The risk of salmeterol-associated death was higher in African-American (625% increase) than in Caucasian (482% increase) patients, reaching significance when all racial and ethnic groups were assessed

together (337% increase compared with the placebo group).

In their concluding remarks, the authors took note that the study's "imbalance occurred largely in the African-American subpopulation." Also, they wondered if the cause for the racial imbalance was due to "factors including, but not limited to, a physiologic treatment effect, genetic factors, or patient-level behaviors leading to poor outcomes (eg, delay in seeking care, compliance with study treatments or asthma medications)."

What are the facts regarding this issue and do they really matter?

Physiologic and genetic variability has, indeed, surfaced as a significant therapeutic issue in asthma.

Specifically, studies have described racial differences in corticosteroid response (Federico et al. *Chest* 2005; 127:571) and deleterious beta-adrenergic receptor changes that may be more prevalent in more at-risk populations (Drysdale et al. *Proc Natl Acad Sci* 2000; 97:10483).

In the randomized SMART study, it is doubtful, though, that the lower rates of corticosteroid use in African-Americans account for the entirety of the increased risks observed. Even Caucasian asthma-related deaths numbered 6 in the salmeterol group and 1 in the placebo group. However, as purely a sampling of usual asthma care in the United States, doesn't this study's inhaled corticosteroid discrepancy primarily underscore that unequal treatment with respect to "behaviors" is better labeled as "physician-level"?

Asthma care variation and health-care disparities, in general, remain an area of deep concern in the United States (Institute of Medicine. *Unequal Treatment*, National Academy Press, 2002).

The asthma morbidity and mortality burden is shouldered disproportionately by the Hispanic and African-American communities.

However, despite issues of access to and confidence in our health-care system varying greatly, we know that *similar* adherence rates exist across racial and ethnic lines (*Balancing the Equation: Ending Disparities in Health Care Delivery*. www.kaiser.org; Accessed December 2005).

Why, then, would the SMART study authors suggest divergent patient-level factors that include compliance only now appear in African-American (and not Caucasian) patients receiving salmeterol?

Excellence in medical treatment is of no worth if the patient does not take the medication as prescribed. Clinician communication and patient education are vital to a family's compliance with the clinician's recommendations.

Studies consistently show that less than 50% of patients adhere to daily medication regimens.

Furthermore, clinicians cannot predict

Editor's Insight

Perhaps, unfortunately, the SMART trial was not designed to evaluate the concurrent use of LABAs and inhaled corticosteroids, so we cannot really determine the role of the use of LABAs alone without concurrent inhaled corticosteroids as a factor in the increased risk observed in the African-American subpopulation.

We do know, however, that racial disparities confound principles of care. Two-way biases permeate all patient and clinician interactions. Trust is key in the clinician-patient relationships, and it must be earned by the clinician. Effective communication skills and genuine clinician interest for the

patient go a long way in reducing these barriers. Effective individualized, culturally sensitive communication allows patients to understand their asthma and its treatment.

The primary use of corticosteroid inhalers is key. LABAs should never be used as monotherapy (see Global Initiative for Asthma Guidelines at www.ginasthma.com). It is essential that patients understand that increased frequency in the use of either long- or short-acting beta-agonists denotes worsening asthma that may be life-threatening and requires intervention. Education is critical.

—Deputy Editor

Two Questions

I would like to present two questions to underscore two important themes:

1. The following patient/family characteristics are reliably associated with the ability to adhere to your prescribed asthma therapeutic plan:

- A. Race
- B. Ethnicity
- C. Socioeconomic status
- D. Education level
- E. None of the above (A-D)
- F. All of the above (A-D)

Correct answer: E. Contrary to popular medical belief, clinicians cannot predict better than chance which patients are adhering to the medical regimen. There are many different forms of noncompliance, all of which interrupt or interfere with the opportunity for therapeutic success.

2. Effective communication of asthma education is proven to create all of the following EXCEPT:

- A. Increased office visit times
- B. Improved patient/family self-efficacy
- C. Fewer asthma hospitalizations and emergency department visits
- D. Enhanced patient/family confidence that their concerns have been heard
- E. An opportunity to share significant concerns that may hamper adherence

Correct answer: A. Even "established" clinicians can benefit from learning and refining communication skills, as most patients identify this to be an area where doctors could better their medical care. Specific physician communication techniques are shown to boost family confidence, augment patient self-efficacy, and improve asthma patient long-term outcomes without adding additional time to the office visit.

better than chance which patients will be compliant. Compliance is not reliably associated with family income, parental education level, ethnicity, or race.

Therefore, all patients require proper education communicated in a manner that builds self-confidence and enables adherence to the asthma treatment plan (Clark et al. *Acad Med* 1995; 70:957).

A family's ability to follow preventive or therapeutic recommendations is based on its health beliefs. These beliefs include the following: (1) the extent to which a patient feels susceptible to asthma; (2) the perceived seriousness to the patient's own health; (3) the personal benefits vs the costs of the recommended treatment plan; and (4) the degree of confidence with which they can carry out the requested actions.

Some families resist accepting the diagnosis of asthma because they believe the same crippling fate of a relative may await them or their children. Others may not perceive the disease to be a threat at all (eg, "it's like a cold"), hindering their ability to follow the treatment plan.

Often, families may be too embarrassed to share these beliefs if they feel their disclosure will make them appear foolish or uneducated.

Eliciting underlying fears about the diagnosis and/or treatment regimen may be as, if not more, important than prescribing the proper medicine.

Teaching our colleagues to discuss the safety profile of controller medications using as few medical terms as possible is important.

A conversation about inhaled corticosteroid therapy (with or without combination LABAs) and how these and other medications work to keep asthma "under control" can be both useful and reassuring.

Frank discussion, too, about the real and perceived risks of these medicines invites families to more openly share the concerns that limit their acceptance and

implementation of the treatment plan.

Opportunity for questions reinforces the family's belief that the clinician is listening and, therefore, has the information needed to make a good treatment decision.

Even in susceptible patient groups, proven educational strategies can be efficiently delivered via effective communication during scheduled primary care office visits without adding additional time to the encounter (Brown et al. *Chest* 2004; 126:369).

Despite its limitations, the SMART study clearly points to the pressing need for heightened attention paid to research in our most vulnerable asthma populations.

We are reminded, also, that inattentiveness to new potential dangers within medical therapeutics is ripe opportunity for increasing health-care disparity.

Clearly, we should watch this developing story with great interest and an eye on safety for *all* asthma patients. ■

Dr. Randall W. Brown, MPH
Research Director
Georgia Pediatric Pulmonology Assoc.,
PC
Atlanta, GA

Adjunct Associate Professor
Health Behavior and Health Education
University of Michigan School of Public
Health
Ann Arbor, MI

Dr. Deborah Shure, Master FCCP
Editor,
Pulmonary Perspectives

Dr. Aymarrah Robles, FCCP
Deputy Editor,
Pulmonary Perspectives

NEWS FROM THE COLLEGE



PRESIDENT'S REPORT

2006: Our Most Successful Caucus

I seem to do most of my Presidential editorial writing in airports. It is a good use of idle time. While others enjoy the sport of arriving just before the door is closed, I would rather not chance missing my flight home, but that's not the subject of this month's column.

I am in Reagan National Airport, awaiting my return flight to Tampa after attending the 13th Annual ACCP Capitol Hill Caucus. It is a well-worn cliché, but the Caucus just gets better every year (and this year, as in others, it's true).

I feel qualified to comment, as I have attended all but one of the caucuses. This year's attendance, including ACCP staff, topped 100, which is more than double the attendance in 2005. Don't

miss coverage of the Caucus in this issue of *CHEST Physician*.

I will begin and end this column by suggesting that you consider attending the 14th Annual Caucus in 2007.



BY DR. W. MICHAEL ALBERTS, FCCP

Credit for the fast-paced and educationally dense program goes to the Government Relations Committee, chaired by Dr. Larry C. Mohr, Jr., FCCP, and the Health Affairs Division, headed by Lynne Marcus.

This year, the Government Relations Committee decided to concentrate on two issues: the sustainable growth rate formula, more affectionately known as the "unsustainable growth rate" formula, and the critical care medicine workforce crisis.

The first afternoon of the Caucus was directed at providing attendees

with background information on these issues. In addition, a consultant provided instruction on "how to lobby your elected official," in anticipation of the planned Capitol Hill visits.

The role-playing exercise was entertaining and proved valuable during the next day's visits.

Our dinner speaker that evening was the US Surgeon General, Dr. Richard H. Carmona, MPH. If you ask any of the attendees about the highlights of the Caucus, I bet they mention the Surgeon General. He is about as personable as you can get, and he gave a spellbinding talk. The country's health is in good hands with Dr. Carmona.

The next morning, through the assistance of Senator Bill Nelson of Florida, we were able to secure the very remarkable and historic Senate Caucus Room in the Russell Building (where

the Watergate hearings were held). A very impressive list of House and Senate members (including Representative Stark, Senator Crapo, and Senator Clinton) dropped by to provide their views on our two main issues and on a few of their own.

That afternoon, attendees visited the offices of their Representative and Senators. More often than not, attendees met with staff, but, as we were reminded, "Do not underestimate the influence of staff on the views and votes of the members." Sharing these experiences on the hill, during and after dinner, was among the favorite activities of many attendees.

As promised, let me close by encouraging you to attend the 2007 Capitol Hill Caucus. Participating in the democratic process and walking the Halls of Congress is both energizing and a lot of fun. ■

Inside the ACCP: *CHEST* Reaches Around the Globe

As the ACCP's flagship publication, *CHEST* has and continues to reflect the interests of the ACCP membership.

BY STEVE WELCH
Vice President, Publications
Executive Editor, *CHEST*

CHEST is the official journal of the American College of Chest Physicians (ACCP) and is considered by many to be the top clinical journal in its multidisciplinary fields. *CHEST*'s success is a result of 70+ years of dedicated leadership and vision by ACCP and the journal's Editors in Chief (Table) and Editorial Board members.

Initially launched in 1935 under the name *Diseases of the Chest* by the American Federation of Sanatoria (which

became the ACCP in 1937), the journal focused on educating physicians about tuberculosis, the leading lung scourge at the time. As the development of powerful antibiotics controlled TB, the journal broadened its focus to cover the multidisciplinary nature of chest medicine.

In 1970, under the leadership of Dr. Alfred Soffer, Master FCCP, the journal's name was shortened to *CHEST*.

As the ACCP's flagship publication, *CHEST* has and continues to reflect the interests of the ACCP membership.

Over time, it has evolved from a publication that

focused on surgical interventions for TB to a multidisciplinary publication that covers pulmonary, critical care, sleep, thoracic surgery, cardiorespiratory interactions, and related disciplines.

The journal's vital statistics show it to be a leader in numerous ways.

CHEST has: (1) the highest regular annual circulation/readership (eg, 20,450) of any respiratory or critical care journal in the world; (2) increasing annual manuscript submissions (from 2,080 in 1994 to 3,368 in 2005); (3) a steadily falling annual acceptance rate (from 43% in 1993 to 17% in 2005); (4) the second highest number of total citations of 31 respiratory journals; (5) an impact factor of 3.11 and rising; (6) increasingly high profile coverage in major media outlets each month; and (7) excellent financial performance, which helps to support many ACCP activities.

And because *CHEST* is financially stable and is committed to supporting the educational mission of the ACCP, it remains one of the least expensive medical specialty journals; this facilitates its

CHEST Editors in Chief

1935–1937 Dr. Charles M. Hendricks, FCCP
1937–1941 Dr. Frank W. Burge, FCCP
1941–1946 Dr. Ralph C. Matson, FCCP
1946–1968 Dr. Jay Arthur Myers, FCCP
1968–1993 Dr. Alfred Soffer, Master FCCP
1993–2005 Dr. A. Jay Block, Master FCCP
2005– Dr. Richard S. Irwin, FCCP

accessibility to subscribers, libraries, and institutions around the globe.

CHEST is truly an international journal. Of its 3,368 submissions in 2005, 33% were from the US; 4%, Canada; and 63%, the rest of the world. And of those accepted and published, 30% were US, 5% Canada, and 65% rest of the world.

In addition, it is distributed to more than 100 countries around the world and distributes special international editions translated into local languages in China, Italy, Mexico, Latin America, Spain, and Turkey, with more to come. There is also a special English edition distributed in India.

The online edition of *CHEST*, www.chestjournal.org, is hosted by HighWire Press, a division of the Stanford University Library Systems.

The online edition offers numerous technology

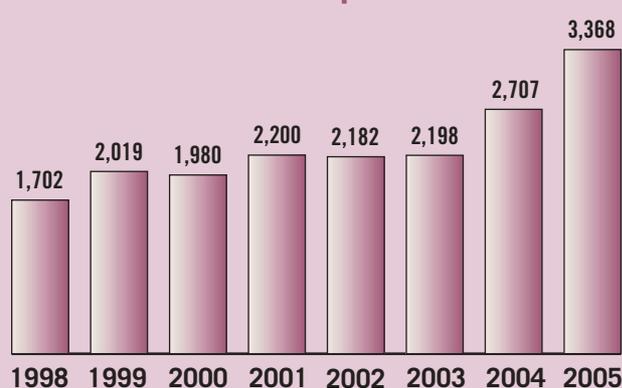
enhancements that allow users and readers to search its vast archive and PubMed; link to articles in *CHEST* and other journals; download material to handheld devices; build an online "article archive" that puts online articles at their fingertips; download figures into PowerPoint for use in lectures or reports; and use many other useful tools.

CHEST is committed to increasing these enhancements in the future.

Under the current leadership of Editor in Chief Dr. Richard S. Irwin, FCCP, *CHEST* has already undergone significant changes and is poised to continue its push to be the most relevant and read journal in its multidisciplinary fields.

We encourage our readers to give us feedback on the journal at any time and thank them for their support and suggestions.

Feedback can be sent to editor@chestnet.org. ■

CHEST Manuscript Submissions

Source: American College of Chest Physicians

NEWS FROM THE COLLEGE



SLEEP STRATEGIES

Tin Soldiers and Capped Rental Coming: New Regulations for CSA

For those of you who deal with durable medical equipment (DME), this nostalgic Neil Young paraphrased title is intended to inform those interested about big reimbursement changes coming. This applies to providers, prescribers, and caregivers of home nocturnal noninvasive ventilation (NIV) patients who are beholden to the latest Centers for Medicare and Medicaid Services (CMS) payment methodology for all respiratory assist devices (RADs). The reimbursement for ongoing long-term attention to needy NIV patients (especially those for neuromuscular disease) provided by the "frequent and substantial servicing (FSS)" payment category will eventually disappear with the reclassification to the "capped rental" category. There are also new coverage criteria for patients with central sleep apnea (CSA). What does all this mean?

CMS published a final regulation in the January 27, 2006, Federal Register notice (<http://a257.g.akamaitech.net/7/257/2422/01jan20061800/edocket.access.gpo.gov/2006/pdf/06-798.pdf>) that would shift payment for all RADs with a backup rate (EO471) from the prior "FSS" to the "capped rental" category. Under the FSS payment schema, CMS paid out as long as the beneficiary required the device. With the "capped rental" payment plan, this continues for 13 months in a rent-to-own process (similar to what CPAP is now). Several societies, including the ACCP, American Thoracic Society (ATS), and NAMDRRC, have been trying to prevent this payment shift for several years. The FFS category was sustained, in part, because the Food and Drug Administration (FDA) refers to the RADs with a backup rate as a therapeutic ventilator (such as a portable home ventilator), and this designation justified the FSS categorization, even for CMS. The CMS effort to simply rename the EO471 as just another RAD for payment purposes seemed to contradict the Medicare statute as stated by the FDA.

With the endorsement of the ACCP and ATS, NAMDRRC arranged a meeting on March 6, 2006, at the office of Senator Mike Crapo (R-ID), Chair of the Congressional COPD Caucus, in conjunction with representatives from the FDA, CMS, and Health and Human Services (HHS). Neil MacIntyre, MD, FCCP; Nick Hill, MD, FCCP, and I indicated concern that there is a wide variety of diseases and severity of condition for which patients are prescribed an EO471 device for home NIV, some of which need frequent reassessment of the patient-ventilator interaction. As the discussion evolved, an effort was made to clarify that it is the

application to the clinical condition that really determines what makes a device a "therapeutic ventilator," as the RADs have been and are being used even on patients with a tracheostomy that all would agree makes the device a "therapeutic ventilator" by the CMS language used in the January 27, 2006, Federal Register cited above. The point was further emphasized that

if you focus entirely on the device to describe the situation, it can lead to clinically misleading presumptions about the therapy. Unfortunately, there is no true definition for the terminology of "therapeutic ventilator" or "respiratory assist device." If decisions for servicing and payment remained focused on just the device, it is possible that clinicians might switch patients to more sophisticated and expensive home portable ventilators to obtain the FSS reimbursement for a higher care delivery result. Presumably, the manufacturers could also follow suit and alter the RADs to have more of an appearance of a "therapeutic ventilator."

The conclusion of the meeting was to have HHS review this FSS issue with their General Counsel's office and decide whether there is enough flexibility to revisit the interpretation of the present statute. We hope it will allow some reasonable clinical criteria to enter into the determination of a patient's reimbursement status and not depend solely on the type of device. If this is affirmed, then select members of the pulmonary/sleep community may be called upon to create criteria and patient scenarios. If there is a denial of this possibility, Senator Crapo is then committed to help solve the problem legislatively. The attendees decided 60 days would be a reasonable time frame for the General Counsel to respond and also allows plenty of time to create legislation before the first capped rental process is in effect, as the 13-month period comes up on May 1, 2007 (assuming that the regulation goes into effect on April 1, 2006).

A very advantageous alteration in the coverage criteria for patients with CSA was also announced with the above. The previous coverage criteria for CSA were burdened by the mandatory hypoxemia requirement restricting patients with major sleep disruption from CSA but minimal oximetry reduction to the sole option of CPAP. At the initiation of sleep specialists at the Mayo Sleep Disorders Center, a proposal was brought forth to the three newly designated DME Regional Carrier or DMERC directors, who now include Drs. Paul Hughes, Mark Pilley, and

Adrian Oleck. As a result, a revised coverage position emerged, eliminating the inappropriate oximetry requirements and also recognizing the problem encountered when patients with qualifying obstructive or mixed sleep apnea develop

significant CSA when exposed to CPAP. The patients that develop new or very prominent CSA during CPAP titration are now designated as

"complex sleep apnea" or CompSA. The new criteria only demand that the patients have a facility-based polysomnogram and receive a diagnosis of either (a) predominate (>50%) CSA with at least five events per hour, or (b) CompSA. They must fail the CPAP titration and show a "significant improvement" with an EO471 device, and, then, it can be prescribed. This can be a bilevel device

with a backup rate or a newly approved ventilator (Adapt Servo Ventilator; ResMed; Poway, CA) designed for these patients. The new criteria and definitions are actually retroactive to January 1, 2006, and can be viewed at the DMERC carrier Web site for your region and at the following Web site: [www.palmettogba.com/palmetto/providers.nsf/\(Docs\)/85256D580043E75485256A6F0055769A?OpenDocument](http://www.palmettogba.com/palmetto/providers.nsf/(Docs)/85256D580043E75485256A6F0055769A?OpenDocument). There is still the requirement for follow-up, stating that the patient sees benefit from continued use of the device and is using it at least 4 hours a night. This new set of criteria should allow many more difficult-to-treat patients with CSA or CompSA to obtain needed therapy. ■

Dr. Peter C. Gay, FCCP
Associate Professor of Medicine
Pulmonary, Critical Care, and Sleep Medicine
Mayo Clinic, Rochester, MN

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NEWS FROM THE COLLEGE



EDUCATION INSIGHTS

The ABCs of Grading Evidence-Based Clinical Practice Guidelines

BY CARLA HERRERIAS, MPH
Clinical Research Analyst
ACCP Health and Science Policy

With the publication of Grading Strength of Recommendations and Quality of Evidence in Clinical Guidelines: Report From an American College of Chest Physicians Task Force,¹ in the January 2006 issue of *CHEST*, the ACCP Health and Science Policy department has implemented a new grading system for guideline recommendations.

This system is based on the relationship between the strength of the evidence and the balance of benefits to risks and burdens (Table). In this simplified system, recommendations can be grouped into two levels, **strong** (grade 1) and **weak** (grade 2). If there is certainty that the benefits do (or do not) outweigh the risks, the recommendation is strong. If there is less

certainty, or if the benefits and risks are more equally balanced, the recommendation is weak. Several important

issues should be considered when classifying recommendations, including (1) the quality of the evidence that supports estimates of benefit and risk; (2) the importance of the outcomes of an intervention; (3) the magnitude and the precision of the estimate of the treatment effect; (4) the risk or burden of an intervention therapy; (5) the risk of the target event; and (6) patient values and preferences.

The strength of evidence is classified into three categories: high (**grade A**), moderate (**grade B**), and low (**grade C**), based on quality of the data abstracted

Relationship of Strength of the Supporting Evidence to the Balance of Benefits to Risks and Burdens

Strength of Evidence*	Balance of Benefits to Risks and Burdens			
	Benefits Outweigh Risks/Burdens	Risks/Burdens Outweigh Benefits	Evenly Balanced	Uncertain
High	1A	1A	2A	...
Moderate	1B	1B	2B	...
Low or very low	1C	1C	2C	2C

*1A, 1B, 1C = strong recommendation; 2A, 2B, 2C = weak recommendation.

from the literature. The strongest evidence comes from well-designed, randomized, controlled trials, with consistent and directly applicable results. Moderate, quality evidence is based on randomized, controlled studies, with limitations that may include methodologic flaws and/or inconsistent results. In some circumstances, consistent evidence from observational and other nonrandomized studies may also be included. The weakest type of evidence comes from other types of observational studies, which, when used appropriately, can provide additional data. It should be noted that the ACCP Health and Science Policy Committee accepts the principle that most relevant clinical studies from peer-reviewed publications provide evidence, even though the quality of that evidence may vary. Therefore, the criteria for including and excluding studies should be explicitly explained in each clinical practice guideline.

The balance between the benefits and the harms, or the lack thereof, helps determine the strength of the

recommendation. A greater certainty of the balance leads to a stronger recommendation. Patient and community preferences are important considerations in decision-making and, therefore, are factored into the grading process. For weaker recommendations, there may not be much consistency in patient preferences. For strong recommendations, patient values may be very much aligned.

This new grading system eliminates the potential for misinterpreting guideline recommendations by basing recommendations strictly on the strength of evidence and balance of benefits and harms. The Health and Science Policy Committee hopes to maintain consistency by implementing this method for all ACCP clinical practice guidelines. For more information, go to www.chestnet.org/education/guidelines/index.php.

1. Guyatt G, Gutterman D, Baumann MH, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians task force. *Chest* 2006; 129:174-181

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ACCP Product Highlights:
Online Education Site

The ACCP online education site opens the door to many educational opportunities.

View the newest virtual symposium Webcast, with audio tracks and faculty presentations or monographs from the CHEST 2005 satellite sessions. There are several topics on PAH, such as "Topical Issues and Controversies in the Treatment of Pulmonary Arterial Hypertension," and "The Changing World of Pulmonary Arterial Hypertension Therapies: A Focus on the Patient," to list a few. Education opportunities in asthma and COPD are also available. These are all CME opportunities for those who did not claim them for CME at CHEST 2005.

ACCP recognizes the importance of sleep medicine in the pulmonary community. An on-demand Webcast is available, featuring the latest clinical information for effective evaluation, diagnosis, and treatment of sleep apnea. This product includes three video presentations with slides from the 2006 ACCP Sleep Medicine Course and syllabus.

Check out our newest products in the ACCP online store: "Clinical Insight in Practice: COPD," "Clinical Insight in Practice: Asthma," and "Hypertensive Crisis: Strategies To Minimize End Organ Damage With Focus on the Heart and Brain."

For more information, visit www.chestnet.org/education/online.

NEWS FROM THE COLLEGE



ACCP Capitol Hill Caucus: A Unified Voice in Washington

The 2006 Caucus welcomed its largest attendance in history, with participation from 80 ACCP members.

BY JENNIFER STAWARZ
Manager, ACCP Public Relations

Each Spring, members of the American College of Chest Physicians head to Washington, DC, determined to send a powerful message to legislators about pressing issues affecting pulmonary and critical care medicine professionals. This year, the 13th annual ACCP Capitol Hill Caucus proved to be an invigorating and valuable experience for participants, highlighted by the event's record participation and special presentations by the US Surgeon General, Vice Admiral Richard H. Carmona, MD, and New York Senator Hillary Rodham Clinton.

The Caucus is the College's largest annual advocacy initiative, which allows ACCP members to have a unified voice in Washington. Held in early March, the 2006 Caucus welcomed its largest attendance in history, with participation from 80 ACCP members, representing 45 US states, the District of Columbia, and Puerto Rico. Hosted

by the ACCP Government Relations Committee, the Caucus drew members from the ACCP Executive Committee, Board of Regents, Governors, and membership-at-large. Additional participants included 30 ACCP staff members and guests, including three Canadian Governors and representatives from the American Association of Critical-Care Nurses, Society for Thoracic Surgery, American Thoracic Society, and NAMDRC.

Caucus participants were engaged in a solid, 2-day agenda, which included education on issues, lobbying training, discussions with political officials, and culminating with personal appointments with local legislators. Participants were briefed about the important aspects of the Sustained Growth Rate (SGR) in Medicare reimbursement and the impending critical care workforce shortage.

The evening's event featured a compelling and humorous after-dinner discussion with Vice Admiral Richard H. Carmona, MD, Surgeon General of



Dr. James Parish, FCCP, discussed key ACCP issues with Senator Jon Kyl (R-AZ).

the United States, who spoke candidly about his rise from the streets of Harlem, NY, to becoming the 17th US Surgeon General. He emphasized the important role of pulmonary and critical care physicians in US health-care and challenged the ACCP and its members to continue working with government agencies to identify solutions to the SGR formula and workforce shortage issues.

On day two, participants gathered in the historic Senate Caucus Room in the Russell Office Building for a morning of lively debate with government officials and legislators from Arizona, California, Colorado, Georgia, Idaho, and New York. Topics focused on how the current health-care shortage and Medicare physician reimbursement are impacting the delivery of patient care. The morning agenda also included a presentation by New York Senator Hillary Rodham Clinton, who spoke about the Family Asthma Act.

Morning discussions were followed by individual and group appointments with ACCP members' respective Senators, Con-



The US Surgeon General, Dr. Richard H. Carmona, addressed the Caucus.

gressional Representatives, and legislative staff. More than 240 prearranged meetings allowed ACCP members to speak openly with legislators and health legislative aides. ACCP members urged policy makers to replace the existing SGR formula with one that accurately reflects physician practice costs. In addition, ACCP members requested the release of the long-awaited report from the US Health Resources and Services Administration (HRSA), outlining the inadequacy of the pulmonary and critical care physician workforce supply to meet the demand for critical care services.

A wrap-up dinner and discussion gave participants an opportunity to share their individual experiences and observations about the Caucus. Larry Mohr, MD, FCCP, Chair of the Practice Management Committee, emphasized to participants that this was their Caucus, that their participation in the political process made an impact on the important issues that were addressed, and that individual follow-up with legislators was important for sustaining the momentum produced in Washington.

ACCP members are encouraged to participate in the 2007 Capitol Hill Caucus, to be held March 5-6, 2007. For more information or to learn how to contact your local legislators, contact Lynne Marcus at (847) 498-1400 or e-mail lmarcus@chestnet.org.



Senator Hillary Rodham Clinton (D-NY) spoke to attendees about health reform.



Left to right: Al Lever, ACCP CEO and Executive VP; Sen. Clinton; Dr. W. Michael Alberts, FCCP, ACCP President; Lynne Marcus, ACCP VP of Health Affairs; Dr. James Parish, FCCP, Past Chair of the ACCP Government Relations Committee; Dr. Lawrence Mohr, Jr., FCCP, Chair of the Government Relations Committee.

Caucus Attendees Share Their Views

First Attendee Impression

"My first attendance at the ACCP annual Capitol Hill Caucus was a very insightful one. It gave me the opportunity to understand the complex interplay of political decision-making and the impact it has on the day-to-day care of our patients.

I have come to realize that in order to make an impact in the decision making process with regard to our issues of interest, every member of the College needs to establish a relationship with his/her representative and campaign to meet our patients' needs.

We need to make it OUR responsibility to keep our legislators continually informed of the issues that confront us

and our medical perspective in political decision-making."

Dr. Prasad N. Betadpur, FCCP

An ACCP Governor Reports

"As the Arizona Governor for the ACCP, I wanted to relay to all of you what the ACCP is doing on behalf of its members, which includes specialists in pulmonary, critical care, cardiology, and thoracic surgery and many allied health members.

The Capitol Hill Caucus was a very positive event in raising awareness of issues that are important to members of our College. I would encourage all of you to call or write your Representatives and Senators. The College offers

you a software program called Cap Wiz that makes it very easy to send an e-mail to members in Congress.

Go to the ACCP Web site (www.chestnet.org), and click on Practice Resources, then Government Relations, and enter your home zip code."

Dr. Jim Parish, FCCP

Canadian Governors Enlightened

"We were impressed with the presentations given by the Congressmen, Senators, and legislative staff, and the grasp of the issues that they displayed during the question and answer sessions. We appreciated the politicians' candor and willingness to disagree with us.

Our medical system is very different, but Canadian respiratory physicians face many of the same problems, issues, and

challenges. Hopefully, we will be able to apply the lessons learned in Washington to effectively advocate for the issues facing respiratory medicine in Canada.

We will need to educate the legislators and the public to direct them to appropriate solutions.

Our Capitol Hill experience will help us lobby for more support for innovative care at the provincial level and for more research support from the lung associations, other nonprofit organizations, and from both the provincial and federal governments.

We will strongly encourage the Canadian governors to attend future Capitol Hill caucus meetings."

*Dr. S.K. Field, FCCP;
Dr. S. Sharma, FCCP; and
Dr. N.J.D. Duguid, FCCP*

NEWS FROM THE COLLEGE



TB, Aerosol Devices, Dyspnea—NetWorks Tackle Timely Topics

Affiliate NetWork

The Affiliate NetWork Steering Committee is working on a number of activities for CHEST 2006. Submissions for case reports have been made, and the grading process is now underway.

The 2006 CHEST Challenge will provide affiliate members a chance to participate in the Jeopardy-style competition. Nine teams will be selected to participate in the final rounds at CHEST 2006. The teams selected will receive roundtrip airfare, hotel accommodations, and meeting registration. The winning team will be awarded \$5,000. Participation is open to affiliate members currently in training. For more details, go to www.chestchallenge.org. We invite you to visit the NetWork Web page, at www.chestnet.org/networks/affiliate/index.php.

Airways Disorders NetWork

Inhaled beta-2-agonists have been used to treat asthma for more than 40 years. Long-acting beta-agonists (LABAs)

provide sustained bronchodilation and improved asthma control when used in the long-term treatment of persistent asthma. However,

the long-term safety of LABAs has recently been questioned. The SMART study (CHEST, January 2006) revealed a small, but statistically significant, increase in the incidence of adverse asthma and respiratory experiences in asthmatics.

Currently, the Pulmonary-Allergy Drugs Advisory Committee of the Food and Drug Administration (FDA) require warnings that state, "These medicines may make asthma episodes more severe when they occur," and the committee warns against their use in

first-line asthma therapy, unless other medicines alone do not control the disease. This advisory conflicts with the

current asthma treatment guidelines, creating confusion among health-care workers and patients. Studies are underway to determine the genetic variability in use of these drugs.

Allied Health NetWork

To make things happen in an area of need, the Allied Health NetWork has found that the best projects are those done in collaboration

with other NetWorks. One such program is the Inhaled Aerosol Device Project. Arguably, the management of asthma and COPD is 10% medication and

90% education. Researchers report that between 23 and 68% of patients, who are prescribed aerosol devices, do not use them well enough to benefit from their use. This represents up to \$7 billion health-care dollars wasted each year.

To address this problem, the Allied Health NetWork joined forces with the Airways Disorders, Home Care, and Respiratory Care NetWorks to produce handouts that show how to properly use and maintain specific inhalers and nebulizers. David Vines, RRT, Dr. Jay Peters, FCCP, James Fink, MS, RRT, and Dr. Paula Anderson, FCCP, worked with a number of collaborators to produce a series of 16 handouts, available on the ACCP Web site, at www.chestnet.org/patients/guides/inhaledDevices.php.

Cardiovascular Medicine and Surgery NetWork

Dr. Jean Buithieu, Director, Echocardiography and Noninvasive Cardiology, McGill University, Montréal,

Continued on following page



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SALT LAKE CITY

NEWS FROM THE COLLEGE

AMERICAN COLLEGE OF
CHEST
PHYSICIANS*Continued from previous page*

Canada, spoke on the role of cardiac imaging in the ICU at our CHEST 2005 NetWork meeting.

The following is a very brief summary:

Cardiac imaging modalities increasingly bring valuable information to the ICU clinician. Bedside transthoracic echocardiography (TTE) is indicated to rule out infective endocarditis, aortic dissection, sources of embolus, and to work up unexplained hypoxemia and hemodynamic instability.

Bedside transesophageal echocardiography (TEE) complements TTE limitations due to sub-optimal imaging conditions from obesity, COPD and interfering surgical wounds, dressing, and drains. It presents superior sensitivity in the diagnosis of left atrial appendage thrombus, valvular vegetation, abscess and prosthetic dysfunction, aortic dissection, and localized tamponade.

Nuclear cardiology imaging can also provide data about global and regional systolic function and the presence of myocardial perfusion defects.

As radionuclide imaging, coronary angiography and percutaneous coronary intervention, cardiac CT, and MRI currently require intrahospital transport, their integration in routine ICU patient care may benefit from redesign of future ICU space and patient flow.

Chest Infections NetWork

The ACCP Council of Committees recently approved a NetWork project, entitled Diagnosis and Treatment of Latent Tuberculosis (TB) Infection and Active TB in Non-HIV Immunosuppressed Patients, led by Dr. Patricio Escalante, FCCP.

The aim of this project is to develop a systematic review that addresses this controversial subject. The Delphi method will be used to reach consensus among a panel of TB experts.

A steering committee will prepare a questionnaire with proposed diagnostic and treatment options for this patient population, based on available scientific data. The questionnaire will be distributed to the experts, who will report back to the steering committee in three cycles. The steering committee will then measure the degree of agreement with each recommendation.

The opinions of the expert panel and the level of consensus will be reported.

This project will identify diagnostic and treatment options with a high level of acceptance among TB experts and chest

physicians, as well as areas in need of further research.

Clinical Pulmonary Medicine NetWork

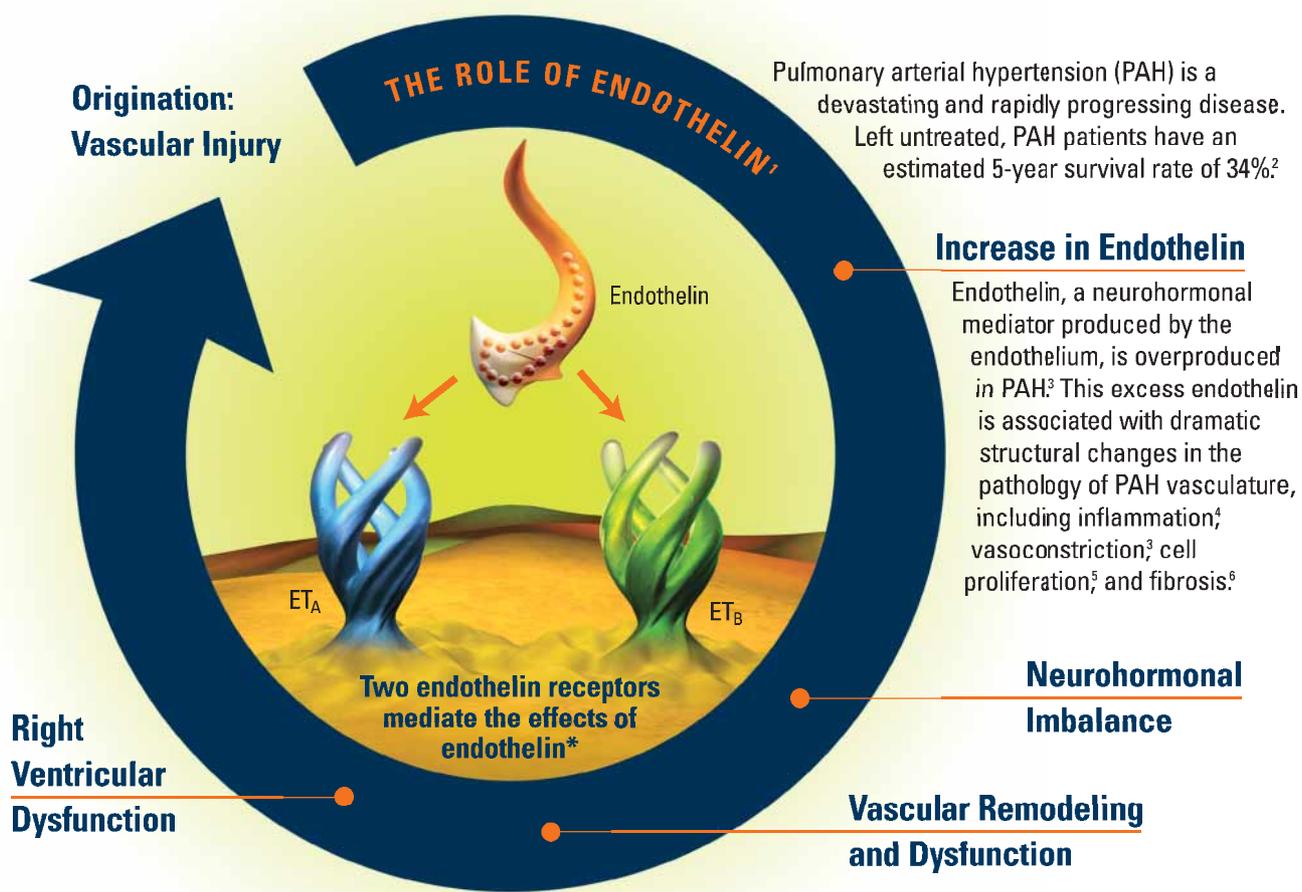
A Web-based patient education brochure on dyspnea is being developed by the Clinical Pulmonary Medicine NetWork. "Dyspnea is a common problem for the pulmonologist to evaluate," says Dr. Jeana O'Brien, FCCP, Chair of the Clinical Pulmonary Medicine Steering Committee.

"Patients with this problem will typically undergo many tests looking for the cause for their shortness of breath. The dyspnea brochure helps explain these tests and why they are being ordered, using words understandable for most patients." A multidisciplinary scientific workshop, Detection and Management of Depression and Anxiety in COPD, will take place at the ACCP headquarters in Northbrook, IL, on September 15 and 16, 2006. This cooperative

review of best practice standards and examination of patient care issues will help identify research needs, direct future studies, and assist clinicians in better diagnosis and treatment of patients with COPD. Dr. Janet Maurer, FCCP, is Chair, and Dr. Nicola Hanania, FCCP, is Co-Chair of the workshop.

To register, go to www.chestnet.org/education/courses/dmdaCOPD06/index.php.

Endothelin's Role in the Rapid Progression of Pulmonary Arterial Hypertension



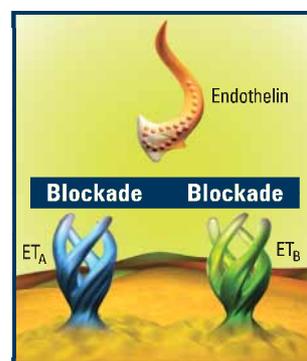
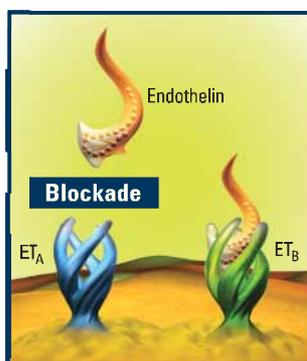
Blockade of Both ET_A and ET_B Receptors Is Critical

ET_A Activity in PAH*

Cell proliferation⁵
Vasoconstriction³
Inflammation⁴

ET_B Activity in PAH*

Cell proliferation⁵
Vasoconstriction³
Inflammation⁴
Fibrosis⁶
Hypertrophy⁶



To learn more about the effects of endothelin in pulmonary arterial hypertension, please visit www.endothelinscience.com

*Statements are based on observations reported from in vitro or animal trials.

1. Gaine SP, Rubin LJ. Primary pulmonary hypertension. *Lancet*. 1998;352:719-725. 2. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med*. 1991;115:343-349. 3. Miyauchi T, Masaki T. Pathophysiology of endothelin in the cardiovascular system. *Annu Rev Physiol*. 1999;61:391-415. 4. Muller DN, Mervaala EM, Schmidt F, et al. Effect of bosentan on NF-kappaB, inflammation, and tissue factor in angiotensin II-induced end-organ damage. *Hypertension*. 2000;36:282-290. 5. Davie N, Haleen SJ, Upton PD, et al. ET(A) and ET(B) receptors modulate the proliferation of human pulmonary artery smooth muscle cells. *Am J Respir Crit Care Med*. 2002;165:398-405. 6. Gaiad A, Yanagisawa M, Langbein D, et al. Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. *N Engl J Med*. 1993;328:1732-1739.



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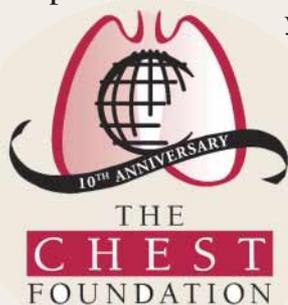
NEWS FROM THE COLLEGE



Second Critical Care Medicine Distinguished Scholar Award

All ACCP members who are active Fellows and board-certified in critical care medicine are invited to apply for the Second Eli Lilly and Company Distinguished Scholar in Critical Care Medicine award. **Deadline for applications is May 31, 2006.**

The successful candidate is required to meet one or more of the goals established for the Second Distinguished Scholar in Critical Care Medicine. These goals include: (1) establish an identity for the diagnosis and management of diseases in a critical care environment; (2) promote alternatives for the treatment of critical care diseases; (3) educate patients about options for diagnosis and management; (4) educate and disseminate new knowledge about diagnosis and treat-



ment within a critical care environment; and (5) address family, legislative, and regulatory issues and define new funding mechanisms leading to innovations and improvement in critical care. The successful candidate will serve for 3 years as the Second Eli Lilly and Company Distinguished Scholar in Critical Care Medicine and receive a stipend of \$50,000 to develop a project. In the fourth year, a stipend of \$10,000 will be given as he or she serves in the role as mentor to the next Distinguished Scholar.

Go to www.chestfoundation.org, and click on the Second Eli Lilly and Company Distinguished Scholar in Critical Care Medicine. Direct questions to Sue Ciezadlo at sciezadlo@chestnet.org.

Salt Lake City: Live It Up

Salt Lake City's family-oriented attractions offer plenty of fun for adults and children throughout the day. When the sun sets, the fun heats up even more. Salt Lake City's clubs and nightspots provide entertainment options from jazz and blues to country western line dancing to rock. Going out for drinks in Salt Lake City is just like going out anywhere in the US. Salt Lake City has bars, brewpubs, and restaurants that serve liquor 7 days a week. The only difference you may encounter is that some bars are considered private clubs and charge a nominal membership fee—\$4 for a 2- or 3-week period—rather than a cover charge. Many restaurants and bars are located downtown, within walking distance of the Salt Palace Convention Center. If you want to venture farther, the easy-to-use TRAX light-rail service



can take you where you want to go.

With over 700 daily flights to Salt Lake City, it will be easy to get to CHEST 2006. International travelers may need a visa to enter the United States and should contact the US Immigration Department (www.usimmigrationsupport.org) or the US Customs & Border Protection (www.cbp.gov) for details. For more information, visit www.visitsaltlake.com.

National Critical Care Awareness And Recognition Month

The ACCP commends its members and other dedicated professionals who care for critically ill patients. In honor of their efforts, May has been designated National Critical Care Awareness and Recognition Month. This observance acknowledges the dedication and commitment that critical care teams demonstrate while caring for patients and their families.

The ACCP supports critical care professionals by offering relevant education courses and products throughout the year. Critical care is a primary focus at the annual CHEST meeting and is a featured curriculum topic area for CHEST 2006. In addition, The CHEST Foundation offers honor and research awards to recognize and fund projects that are advancing critical care.

The CHEST Foundation and the

ACCP closely monitor critical care practices and actively develop programs to help improve patient care.

The Critical Care Family Assistance Program is a groundbreaking program that offers educational and support resources to enhance communication in the ICU and to create better outcomes for everyone. Partnering with other professional societies to form the Critical Care Collaborative, the ACCP's Critical Care Institute has joined forces with over 100,000 health-care professionals to help create new patient care models for the critically ill patient that will enable deliverance of effective, efficient patient-focused care.

To view critical care resources available from the ACCP and The CHEST Foundation, visit www.chestnet.org or www.chestfoundation.org.

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Editor's Picks: This Month in CHEST

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



► Evaluation and Outcome of Young Children With Chronic Cough

Dr. Julie Marchant, et al

► Causes and Clinical Features of Subacute Cough

Dr. Nam-Hee Kwon, et al

► Effect of Study Setting on Anticoagulation Control: A Systematic Review and Metaregression

Dr. Carl van Walraven, et al

► Ciclesonide Reduces the Need for Oral Steroid Use in

Adult Patients With Severe, Persistent Asthma

Dr. Eric Bateman, et al

► Transbronchial Biopsy in Usual Interstitial Pneumonia

Dr. Ema Berbescu, et al

www.chestjournal.org

Postop Cognition Dip Tied to Inflammatory Markers

BY DOUG BRUNK
Elsevier Global Medical News

SAN DIEGO — Increased levels of C-reactive protein and other markers of perioperative inflammatory response are associated with neurocognitive decline following cardiac surgery, Dr. Basel Ramlawi said at a congress sponsored by the Association for Academic Surgery and the Society of University Surgeons.

Dr. Ramlawi and his associates prospectively evaluated 41 patients who underwent coronary artery bypass graft and/or valve procedures that used cardiopulmonary bypass. The patients' mean age was 67 years.

All patients had neurocognitive testing preoperatively, postoperatively at day 4, and at 3 months. The validated tests took 45 minutes to administer and covered areas such as memory, executive function, naming, attention, fluency, and premorbid intelligence, said Dr. Ramlawi, who is with the division of cardiothoracic surgery at Harvard Medical School, in Boston.

THE LEVEL OF TAU PROTEIN WAS INCREASED 78% IN PATIENTS WITH NEUROCOGNITIVE DECLINE, COMPARED WITH 29% IN THOSE WITHOUT SUCH DECLINES.

Neurocognitive decline was defined as performing one standard deviation from baseline on at least 25% of tasks.

Study participants also underwent serum testing preoperatively, again postoperatively at 6 hours, and again at 4 days. Levels of C-reactive protein (CRP) and of interleukin 1 β , IL-6, and IL-10 were assessed, and an increase of serum tau protein after surgery was used as a marker of axonal central nervous system damage.

Of the 41 patients, 7 (17%) developed neurocognitive decline. Baseline characteristics and predictors of neurocognitive decline such as age, education level, and perioperative temperature did not differ significantly between patients with and without postoperative neurocognitive decline.

However, patients who experienced postoperative neurocognitive decline had significantly greater increases of CRP, IL-1 β , and IL-10 than those who had no decline.

In addition, the level of tau protein was increased 78% in patients with neurocognitive decline, compared with a tau protein

level of 29% in their counterparts who did not show neurocognitive decline.

"There exists a significant association [between] the magnitude and persistence of the perioperative inflammatory response and neurocognitive decline in this cohort," Dr. Ramlawi said. "This association is likely mediated by axonal damage."

The incidence of neurocognitive decline can range from 5% to 40% for periods up to 5 years after surgery, he said, adding that the etiology of this complication is not known. "It is likely a multifactorial problem,"

Dr. Ramlawi said. "Several theories have been assessed. The most obvious one is ischemia. Any microemboli might cause this."

Other possible factors in neurocognitive decline include anesthesia, perioperative hypothermia, and low level of education.

"While there have been certain markers of brain injury following cardiopulmonary bypass, very few have been associated with clinical outcomes and neurocognitive decline," he said. "Tau protein, on the other hand, assesses axonal damage and has not been [studied] in cardiac surgery before." ■

Dr. Curt Sessler, FCCP, comments: Postoperative cognitive dysfunction (POCD) is underdiagnosed and thus far remains somewhat of a mystery as to causative factors. Previous research links POCD to factors such as advanced age, longer duration of surgery and anesthesia, cardiopulmonary bypass, infection, and pulmonary complications. This exciting work by Dr. Ramlawi and colleagues provides important links of POCD mechanistically with axonal damage and with systemic inflammation.



The following is a brief summary. Please consult complete prescribing information.

CONTRAINDICATIONS: MAXIPIME[®] is contraindicated in patients who have shown immediate hypersensitivity reactions to cefepime or the cephalosporin class of antibiotics, penicillins or other beta-lactam antibiotics.
WARNINGS: BEFORE THERAPY WITH MAXIPIME (CEFEPIME HYDROCHLORIDE) FOR INJECTION IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS IMMEDIATE HYPERSENSITIVITY REACTIONS TO CEFEPIME, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO MAXIPIME OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES INCLUDING OXYGEN, CORTICOSTEROIDS, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

In patients with impaired renal function (creatinine clearance ≤ 60 mL/min), the dose of MAXIPIME should be adjusted to compensate for the slower rate of renal elimination. Because high and prolonged serum antibiotic concentrations can occur from usual dosages in patients with renal insufficiency or other conditions that may compromise renal function, the maintenance dosage should be reduced when cefepime is administered to such patients. Continued dosage should be determined by degree of renal impairment, severity of infection, and susceptibility of the causative organisms. (See specific recommendations for dosing adjustment in **DOSAGE AND ADMINISTRATION** section of the complete prescribing information.) During postmarketing surveillance, encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, and seizures (see **ADVERSE REACTIONS: Postmarketing Experience**). Most cases occurred in patients with renal impairment who received doses of cefepime that exceeded the recommended dosage schedules. However, some cases of encephalopathy occurred in patients receiving a dosage adjustment for their renal function. In general, symptoms of neurotoxicity resolved after discontinuation of cefepime and/or after hemodialysis.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including MAXIPIME, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis". After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate-to-severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS: General: Prescribing MAXIPIME in the absence of proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. As with other antimicrobials, prolonged use of MAXIPIME may result in overgrowth of nonsusceptible microorganisms. Repeated evaluation of the patient's condition is essential. Should superinfection occur during therapy, appropriate measures should be taken. Many cephalosporins, including cefepime, have been associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy. Prothrombin time should be monitored in patients at risk, and exogenous vitamin K administered as indicated. Positive direct Coombs' tests have been reported during treatment with MAXIPIME. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug. MAXIPIME should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis. Arginine has been shown to alter glucose metabolism and elevate serum potassium transiently when administered at 33 times the amount provided by the maximum recommended human dose of MAXIPIME. The effect of lower doses is not presently known.

Information for Patients: Patients should be counseled that antibacterial drugs including MAXIPIME should only be used to treat bacterial infections. They do not treat viral infections (eg, the common cold). When MAXIPIME is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by MAXIPIME or other antibacterial drugs in the future.

Drug Interactions: Renal function should be monitored carefully if high doses of aminoglycosides are to be administered with MAXIPIME because of the increased potential of nephrotoxicity and ototoxicity of aminoglycoside antibiotics. Nephrotoxicity has been reported following concomitant administration of other cephalosporins with potent diuretics such as furosemide. **Drug/Laboratory Test Interactions:** The administration of cefepime may result in a false-positive reaction for glucose in the urine when using Clinistix[®] tablets. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix[®]) be used.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: No long-term animal carcinogenicity studies have been conducted with cefepime. A battery of *in vivo* and *in vitro* genetic toxicity tests, including the Ames Salmonella reverse mutation assay, CHO/HGPRT mammalian cell forward gene mutation assay, chromosomal aberration and sister chromatid exchange assays in human lymphocytes, CHO fibroblast clastogenesis assay, and cytogenetic and micronucleus assays in mice were conducted. The overall conclusion of these tests indicated no definitive evidence of genotoxic potential. No untoward effects on fertility or reproduction have been observed in rats, mice, and rabbits when cefepime is administered subcutaneously at 1 to 4 times the recommended maximum human dose calculated on a mg/m² basis. **Use in Pregnancy—Teratogenic effects—Pregnancy Category B:** Cefepime was not teratogenic or embryocidal when administered during the period of organogenesis to rats at doses up to 1000 mg/kg/day (4 times the recommended maximum human dose calculated on a mg/m² basis) or to mice at doses up to 1200 mg/kg (2 times the recommended maximum human dose calculated on a mg/m² basis) or to rabbits at a dose level of 100 mg/kg (approximately equal to the recommended maximum human dose calculated on a mg/m² basis). There are, however, no adequate and well-controlled studies of cefepime use in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. **Nursing Mothers:** Cefepime is excreted in human breast milk in very low concentrations (0.5 μ g/mL). Caution should be exercised when cefepime is administered to a nursing woman. **Labor and Delivery:** Cefepime has not been studied for use during labor and delivery. Treatment should only be given if clearly indicated. **Pediatric Use:** The safety and effectiveness of cefepime in the treatment of uncomplicated and complicated urinary tract infections (including pyelonephritis), uncomplicated skin and skin structure infections, pneumonia, and as empiric therapy for febrile neutropenic patients have been established in the age groups 2 months up to 16 years. Use of

MAXIPIME (cefepime hydrochloride) in these age groups is supported by evidence from adequate and well-controlled studies of cefepime in adults with additional pharmacokinetic and safety data from pediatric trials (see **CLINICAL PHARMACOLOGY** section of the complete prescribing information.) Safety and effectiveness in pediatric patients below the age of 2 months have not been established. There are insufficient clinical data to support the use of MAXIPIME in pediatric patients under 2 months of age or for the treatment of serious infections in the pediatric population where the suspected or proven pathogen is *Haemophilus influenzae* type b. IN THOSE PATIENTS IN WHOM MENINGEAL SEEDING FROM A DISTANT INFECTION SITE OR IN WHOM MENINGITIS IS SUSPECTED OR DOCUMENTED, AN ALTERNATE AGENT WITH DEMONSTRATED CLINICAL EFFICACY IN THIS SETTING SHOULD BE USED. **Geriatric Use:** Of the more than 6400 adults treated with MAXIPIME in clinical studies, 35% were 65 years or older while 16% were 75 years or older. When geriatric patients received the usual recommended adult dose, clinical efficacy and safety were comparable to clinical efficacy and safety in nongeriatric adult patients. Serious adverse events have occurred in geriatric patients with renal insufficiency given unadjusted doses of cefepime, including life-threatening or fatal occurrences of the following: encephalopathy, myoclonus, and seizures. (See **WARNINGS** and **ADVERSE REACTIONS** sections of the complete prescribing information.) This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and renal function should be monitored. (See **CLINICAL PHARMACOLOGY: Special Populations, WARNINGS**, and **DOSAGE AND ADMINISTRATION** sections of the complete prescribing information.)

ADVERSE REACTIONS: Clinical Trials: In clinical trials using multiple doses of cefepime, 4137 patients were treated with the recommended dosages of cefepime (500 mg to 2 g IV q12h). There were no deaths or permanent disabilities thought related to drug toxicity. Sixty-four (1.5%) patients discontinued medication due to adverse events thought by the investigators to be possibly, probably, or almost certainly related to drug toxicity. Thirty-three (51%) of these 64 patients who discontinued therapy did so because of rash. The percentage of cefepime-treated patients who discontinued study drug because of drug-related adverse events was very similar at daily doses of 500 mg, 1 g, and 2 g q12h (0.8%, 1.1%, and 2.0%, respectively). However, the incidence of discontinuation due to rash increased with the higher recommend-

INCIDENCE EQUAL TO OR GREATER THAN 1%	Local reactions (3.0%), including phlebitis (1.3%), pain and/or inflammation (0.6%)*; rash (1.1%)
INCIDENCE LESS THAN 1% BUT GREATER THAN 0.1%	Colitis (including pseudomembranous colitis), diarrhea, fever, headache, nausea, oral moniliasis, pruritus, urticaria, vaginitis, vomiting

ed doses. The following adverse events were thought to be probably related to cefepime during evaluation of the drug in clinical trials conducted in North America (n=3125 cefepime-treated patients).

TABLE 1
Adverse Clinical Reactions Cefepime Multiple-Dose Dosing Regimens Clinical Trials—North America

*Local reactions, irrespective of relationship to cefepime in those patients who received intravenous infusion (n = 3048).

INCIDENCE EQUAL TO OR GREATER THAN 1%	Positive Coombs' test (without hemolysis) (16.2%); decreased phosphorus (2.8%); increased ALT/SGPT (2.8%), AST/SGOT (2.4%), eosinophils (1.7%); abnormal PTT (1.6%), PT (1.4%)
INCIDENCE LESS THAN 1% BUT GREATER THAN 0.1%	Increased alkaline phosphatase, BUN, calcium, creatinine, phosphorus, potassium, total bilirubin; decreased calcium*, hematocrit, neutrophils, platelets, WBC

At the higher dose of 2 g q8h, the incidence of probably-related adverse events was higher among the 795 patients who received this dose of cefepime. They consisted of rash (4%), diarrhea (3%), nausea (2%), vomiting (1%), pruritus (1%), fever (1%), and headache (1%). The following adverse laboratory changes, irrespective of relationship to therapy with cefepime, were seen during clinical trials conducted in North America.

TABLE 2
Adverse Laboratory Changes Cefepime Multiple-Dose Dosing Regimens Clinical Trials—North America

*Hypocalcemia was more common among elderly patients. Clinical consequences from changes in either calcium or phosphorus were not reported.

A similar safety profile was seen in clinical trials of pediatric patients (See **PRECAUTIONS: Pediatric Use**).

Postmarketing Experience: In addition to the events reported during North American clinical trials with cefepime, the following adverse experiences have been reported during worldwide postmarketing experience. Because of the uncontrolled nature of spontaneous reports, a causal relationship to MAXIPIME treatment has not been determined.

As with some other drugs in this class, encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, and seizures have been reported. Although most cases occurred in patients with renal impairment who received doses of cefepime that exceeded the recommended dosage schedules, some cases of encephalopathy occurred in patients receiving a dosage adjustment for their renal function. (See also **WARNINGS**.) If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated. Precautions should be taken to adjust daily dosage in patients with renal insufficiency or other conditions that may compromise renal function to reduce antibiotic concentrations that can lead or contribute to these and other serious adverse events, including renal failure.

As with other cephalosporins, anaphylaxis including anaphylactic shock, transient leukopenia, neutropenia, agranulocytosis and thrombocytopenia have been reported. **Cephalosporin-class adverse reactions:** In addition to the adverse reactions listed above that have been observed in patients treated with cefepime, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics: Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, renal dysfunction, toxic nephropathy, aplastic anemia, hemolytic anemia, hemorrhage, hepatic dysfunction including cholestasis, and pancytopenia.

OVERDOSAGE: Patients who receive an overdose should be carefully observed and given supportive treatment. In the presence of renal insufficiency, hemodialysis, not peritoneal dialysis, is recommended to aid in the removal of cefepime from the body. Accidental overdosing has occurred when large doses were given to patients with impaired renal function. Symptoms of overdose include encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures, and neuromuscular excitability. (See **PRECAUTIONS, ADVERSE REACTIONS**, and **DOSAGE AND ADMINISTRATION** sections of the complete prescribing information.)

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