



# CHEST *Physician*

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS



BOB BEVERLY/WVU BIOMEDICAL COMMUNICATIONS

West Virginia University's antimicrobial stewardship program has reduced the use of some antibiotics, explained Dr. Arif R. Sarwari.

## Cooperation Drives Antimicrobial Program

BY JEFF EVANS

*Elsevier Global Medical News*

BETHESDA, MD. — The antimicrobial stewardship program at the Health Sciences Center of West Virginia University, Morgantown, has been successful in reducing resistance in some pathogens, while generating more questions about others, according to Dr. Arif R. Sarwari, the program's director.

In its first 5 years, the program at the tertiary care teaching hospital principally used prospective auditing methods and protocols for antibiotic cycling, coupled with educational strategies, to reduce the use of specific antibiotics and, in some instances, see a drop in rates of resistance.

Such results may not have been

possible without the support and involvement of administrators and clinicians from different specialties, many of whom are members of the university's Antimicrobial Review Subcommittee and participated in the creation of the program. Cooperation is necessary because the interventions needed in various departments may differ and may cross a variety of disciplines, Dr. Sarwari said at an annual conference on antimicrobial resistance sponsored by the National Foundation for Infectious Diseases.

The antimicrobial stewardship program began in 2003 and follows many of the recommendations formulated in guidelines issued by the Infectious Diseases

See **Antimicrobial** • page 2

## Anticholinergics Linked to CV Death, Stroke in COPD

*Meta-analysis findings stir controversy.*

BY PATRICE WENDLING

*Elsevier Global Medical News*

The use of two widely prescribed inhaled anticholinergics significantly increased the risk of cardiovascular death, myocardial infarction, or stroke by about 58% among patients with chronic obstructive pulmonary disease, according to the findings of a meta-analysis involving 14,783 patients.

The findings were reported in the Sept. 24 issue of JAMA (2008;300:1439-50).

During follow-up ranging from 6 weeks to 5 years, cardiovascular death, MI, or stroke occurred in 135 of 7,472 patients (1.8%) receiving either inhaled tiotropium bromide or ipratropium bromide for more than 30 days, compared with 86 of 7,311 patients (1.2%) receiving control therapy (relative risk 1.58). The difference was statistically significant.

However, inhaled anticholinergics did not significantly

increase the risk of all-cause mortality, a secondary outcome of the meta-analysis (2.0% vs. 1.6% for control; RR 1.26).

"Clinicians and patients should carefully consider these potential long-term cardiovascular risks of inhaled anticholinergics in the treatment of COPD, and decide whether these risks are an acceptable trade-off in return for their symptomatic benefits," wrote Dr. Sonal Singh of Wake Forest University, Winston-

A new symposium at CHEST 2008 will address anticholinergic inhaler safety. See page 2 for details.

Salem, N.C., and associates.

In the 17 studies included in the meta-analysis, patients had a diagnosis of COPD of any severity. They had received either inhaled tiotropium or ipratropium or control, which could be placebo or active

See **Anticholinergics** • page 2

### INSIDE

#### Pulmonary Medicine Rhinitis Reaction?

Rhinitis was a strong predictor of adult-onset asthma, a European study suggests. • 5



#### Pediatric Chest Medicine Gender Difference

Airway responsiveness may be more severe in postpubertal females with asthma. • 9

#### Sleep Medicine

#### Pressure Is On

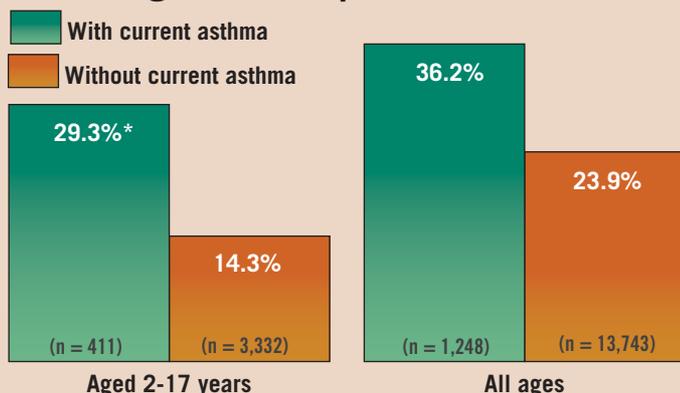
Sleep-disordered breathing may interfere with normal nighttime decrease in systolic blood pressure. • 10

#### Pulmonary Perspectives COPD and Asthma

They may represent disease states along a continuum, with varying degrees of each disease often present in the same patient. • 13

### VITAL SIGNS

#### Influenza Vaccination Utilization Is Higher for People With Asthma



\*Statistically significant compared with children who do not currently have asthma.

Source: 2005-2006 data, Centers for Disease Control and Prevention

## Surgeon General Issues DVT Call to Action

BY DENISE NAPOLI

*Elsevier Global Medical News*

WASHINGTON — Despite progress that has been made in preventing deep vein thrombosis and pulmonary embolism, the persistently high incidence of these conditions has prompted a Call to Action statement by Acting Surgeon General Steven K. Galson.

Among hospitalized spinal cord injury patients who do not receive venous thromboembolism prevention, the risk of developing a deep vein thrombosis (DVT) is 60%-80%. The risk is 40%-60% among similar hip or knee surgery patients, 20%-40% among patients undergoing major general surgery or gynecologic procedures, and 10%-20% for patients with acute illnesses like pneumonia,

according to the Venous Disease Coalition, a network of organizations working to increase public and health professional awareness of venous disease.

The Call to Action statement was issued at the second annual meeting of the Venous Disease Coalition.

"There is now a public acknowledgment that this is a very significant health care issue that deserves attention from multiple

facets of the medical community," Dr. Thomas Wakefield said in an interview. "Although we've known for a long time that this is a very significant problem, since it doesn't belong to one group or another and it spans so many specialties, it has been difficult to mobilize and raise awareness," said Dr. Wakefield, head of vascular surgery at the

See **Surgeon General** • page 4

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## Meta-Analysis Raises Questions

Anticholinergics • from page 1

control, including inhaled  $\beta$ -agonists or inhaled steroid and  $\beta$ -agonist combinations.

Inhaled tiotropium is comarketed in the United States by Boehringer Ingelheim GmbH and Pfizer Inc. under the trade name Spiriva. Ipratropium is available generically and also is marketed by Boehringer Ingelheim as Atrovent.

In a statement, Pfizer and Boehringer Ingelheim said they “strongly disagree with the conclusion reached by Singh et al.” The two companies released a new analysis of 30 controlled clinical trials involving 19,545 patients with COPD. That analysis showed no increased risk of all-cause mortality, cardiac mortality, stroke, or MI ([http://us.boehringeringelheim.com/newsroom/2008/09-23-08\\_spiriva\\_safety.html](http://us.boehringeringelheim.com/newsroom/2008/09-23-08_spiriva_safety.html)).

The analysis includes new data from the industry-sponsored UPLIFT (Understanding Potential Long-Term Impacts on Function With Tiotropium) trial, which appeared online Oct. 5 in the New England Journal of Medicine (see story, p. 7).

Earlier this year, Boehringer Ingelheim informed the Food and Drug Administration that ongoing safety monitoring had identified a “possible increased risk of stroke” in a safety analysis of 29 trials involving approximately 13,500 patients.

The investigators of the current meta-analysis acknowledged that the analysis was limited by the quality of reported data. Many of the trials analyzed were small and short term, resulting in few events. “As a result of small numbers, the 95% [confidence intervals] are wide, resulting in some uncertainty as to the precise magnitude of the observed risk,” Dr. Singh and associates wrote. “None of these trials was specifically designed to monitor the risk of cardiovascular events, which were not adjudicated.”

A sensitivity analysis restricted to the five long-term studies (48 weeks to 5 years) involving 7,267 patients confirmed the significantly increased risk of cardiovascular death, MI, and stroke (2.9% vs. 1.8% for controls; RR 1.73). However, there was no statistically significant increase in these events in a sensitivity analysis of the 12 short-term trials (ranging from 6 weeks to 26 weeks) involving 7,516 patients (0.6% vs. 0.6%; RR 1.16).

The authors reported no financial disclosures. ■

*Information about this topic is provided at [www.chestnet.org/networks/airway\\_disorders/copd.php](http://www.chestnet.org/networks/airway_disorders/copd.php). The ACCP and its Airways NetWork are not offering any opinion now, but are making information available to keep our members informed.*

## Hospital Sees Mixed Results

Antimicrobial • from page 1

Society of America and the Society for Healthcare Epidemiology of America (Clin. Infect. Dis. 2007;44:159-77), said Dr. Sarwari, who is a member of the committee.

It is unclear which combinations of modalities for reducing antimicrobial resistance work best, and “until I have 15 different institutions using 15 different combinations and putting their results out there, how do I know which one works and which one doesn’t? This was our attempt to put out what we think is a sensible approach,” Dr. Sarwari said in an interview.

Although many hospitals have programs to monitor and reduce antimicrobial resistance, most simply restrict the use of certain agents by having one person who approves or denies their use. But West Virginia University prospectively audits antimicrobial use and resistance every 6 months, and implements changes through educational interventions.

Although it was relatively simple to decide to define antimicrobial use through the measurement of defined daily doses per 1,000 patient-days, it took about 6 months of effort to convert data that are captured for billing purposes into data that can be used longitudinally, he said.

Educational programs were established to encourage or discourage the use of select antimicrobial agents, while strategies to promote the use of alcohol-based hand sanitizers were put in place. In addition, the committee made a pocket-card guide available on an educational Web site. The card featured choices of antimicrobials for various clinical scenarios, listed the susceptible proportion of microorganisms that had been identified for that particular year, and gave the top three choices of antimicrobial agents for a particular pathogen (as perceived by the institution).

Interventions centered on the principle of cycling the selection of antimicrobial drugs based on local surveillance of resistance rates, and were tailored for different units of the hospital.

The committee members decided not to keep a very restricted formulary except for quinolones, because more than half of the *Pseudomonas* strains in the ICU were resistant to ciprofloxacin, Dr. Sarwari said.

During 2003-2007, the number of defined daily doses per 1,000 patient-days of quinolones declined by 81%; the same defined measure of ceftazidime declined by 37%, he said. The committee saw a concomitant rise in the use of agents that were designated to replace quinolones and ceftazidime (aminoglycosides and ceftepime, respectively). At the same time, the antimicrobial drug proportion of the pharmacy procurement budget declined from 16% to 8%.

Changes in drug resistance during the period yielded “mixed results,” Dr. Sarwari said. During 2004-2006, rates of ciprofloxacin resistance for *Pseudomonas* declined from 38% to 22% and for *Acinetobacter* from 25% to 0%. In 2007, rates rose again to 34% and 16%, respectively. In the same period, resistance to ciprofloxacin gradually increased in *Escherichia coli* from 7% to 20%. *Klebsiella* resistance to ceftazidime remained stable at about 5%.

The proportion of nosocomial bacteremia cases caused by methicillin-resistant *Staphylococcus aureus* declined from 20% to 10%, whereas rates for bacteremia caused by vancomycin-resistant enterococci held steady at about 7%.

The hospital’s antimicrobial stewardship program “appears to be reasonably successful in affecting institutional use and resistance, but I’m not sure it has [had much] influence on the problem of imported resistance,” Dr. Sarwari said.

In the future, “the big thing we want to try to introduce is some form of molecular microbiology to better get a sense of how many resistant bugs are new strains versus the same strains being passed around due to poor infection control.”

Dr. Sarwari disclosed no conflicts of interest. ■

### CHEST 2008 Late-Breaking Symposium

Monday, October 27, 10:30 a.m.

#### Are Heart Attacks a Side Effect of Anticholinergic Inhalers?

► **Results From the Lung Health Study** (Am. J. Respir. Crit. Care Med. 2002;166:333-9): **Introduction, Dr. Paul Enright, FCCP, Moderator**

► **Results From the Manitoba Health Database** (Int. J. Chron. Obstruct. Pulmon. Dis. 2008; 3:163-9)

► **Results From the National VA Database** (Ann. Intern. Med. 2008; 149:380-90): **Dr. Todd Lee**

► **A Systematic Review and Meta-Analysis** (JAMA 2008;300:1439-50): **Dr. Curt Furberg**

► **Results From the UPLIFT Trial** ([www.upliftcopd.com](http://www.upliftcopd.com)): **Dr. Donald Tashkin, FCCP**

► **Panel Discussion and Rebuttals, With Questions From the Audience**

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## Initiatives Target DVT, PE

Surgeon General • from page 1

University of Michigan, Ann Arbor.

He was one of the roughly 44 physicians and nonphysicians who met with former Surgeon General Richard H. Carmona in May 2006 to urge the medical establishment to help raise awareness of DVT and pulmonary embolism (PE), and to increase research funding. Dr. Galson's Call to Action was a direct result of that meeting, and will "mean great things for the prophylaxis and treatment of this disease," according to Dr. Wakefield.

Along with the Call to Action, the National Heart, Lung, and Blood Institute has awarded 5 years' worth of funding to eight research groups that will investigate venous thromboembolism treatments and prevention—among them, a group to be co-led by Dr. Wakefield.

Other ongoing studies include a multicenter, randomized clinical trial of genotype-guided dosing of warfarin therapy, which is currently the most commonly used treatment for prophylaxis of recurrent venous thromboembolism, according to Dr. Elizabeth Nabel, director of clinical research at the NHLBI (see sidebar).

However, more studies are needed, Dr. Wakefield pointed out, including more studies of newer drugs and pharmacologic

therapies that have less-adverse effects and interactions, and less need for monitoring than has warfarin.

Also worthy of consideration, he said, are studies of short- and long-term outcomes associated with more aggressive interventions for DVT and PE. One such study, which has been funded by the National Institutes of Health and is slated to start soon, will compare pharmacomechanical thrombolysis plus standard anticoagulation versus standard anticoagulation alone for the treatment of significant proximal venous thrombosis.

As of Oct. 1, 2008, any DVT or PE associated with total knee and hip replacement procedures acquired during an inpatient stay will have "payment implications," according to the Centers for Medicare and Medicaid Services.

Just how many patients are affected annually by venous thromboembolism is debated among different groups. Without an autopsy, many cases—perhaps as many as 50%—are misclassified as heart attack, Dr. Wakefield said. According to Dr. Roy S. Silverstein, chair of the committee of government affairs for the American Society of Hematology, the disease affects almost 1 million Americans annually, and

"the estimated number of deaths from PE is higher than the combined number of deaths from breast cancer, HIV disease, and motor vehicle crashes." Dr. Galson put PE- or DVT-related deaths at 100,000 annually, with 350,000-600,000 Americans developing DVT or PE each year. The American Heart Association estimated the

incidence of venous thromboembolism to be 250,000-2 million cases per year (Circulation 2002;106:1436). Meanwhile, upcoming studies put the number somewhere in between.

In any case, Dr. Galson said, "We know that as the U.S. population ages, these numbers are only going to increase." ■

## AHRQ Releases Clot Prevention Guides

Two new booklets aim to help educate patients and physicians on preventing blood clots.

"Your Guide to Preventing and Treating Blood Clots" is a 12-page consumer booklet summarizing the causes and symptoms of clots, ways to avoid them, and what to expect from treatment.

"Preventing Hospital-Acquired Venous Thromboembolism: A Guide for Effective Quality Improvement" is

a 60-page "tool to help hospitals and clinicians implement processes to prevent dangerous blood clots,"

including case studies, according to Dr. Carolyn Clancy, director of the U.S. Department of Health and Human Services' Agency for Healthcare Research and Quality, which published the reports.

Free copies are available by calling 800-358-9295 or by e-mailing [ahrqpubs@ahrq.hhs.gov](mailto:ahrqpubs@ahrq.hhs.gov).

## Warfarin Genotype Study Set to Begin

The National Heart, Lung, and Blood Institute is about to launch its first-ever multicenter, double-blind, pharmacogenetic trial—one focused on warfarin therapy.

The COAG (Clarification of Optimal Anticoagulation Through Genetics) trial aims to determine whether targeting patients according to their genotype during the initiation of warfarin therapy would lead to better and safer anticoagulation control, especially in patients with deep vein thrombosis (DVT), according to an NHLBI representative. Results are anticipated in 2011.

Warfarin is the most commonly used blood-thinning treatment, and the 10th most prescribed medication in the United States, with more than 21 million prescriptions per year, according to the NHLBI.

Patients with certain genotypes metabolize warfarin better than do others, and some researchers believe

there may be an optimal genotype for toleration of the drug.

"It is hoped that prospectively using the genetic information in addition to the clinical information will help clinicians determine better and safer initial dosing for specific patients," an NHLBI spokesperson said.

The COAG trial will be coordinated by the center for clinical epidemiology and biostatistics at the University of Pennsylvania, Philadelphia. By the end of 2008, study coordinators hope to begin enrolling 1,965 patients. Details are still being finalized, but the NHLBI spokesperson said that she expects participants will have to be starting on warfarin therapy with an indication of at least 3 months of treatment. They will likely have to be warfarin naive, and without any major contraindications to anticoagulant treatment.

For more information about patient enrollment, send an e-mail to [dambrauskass@nhlbi.nih.gov](mailto:dambrauskass@nhlbi.nih.gov).

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## Investigational Once-Daily Drug Disappoints in COPD Trial

BY JESSICA MERRILL  
"The Pink Sheet"

Two studies evaluating the efficacy and safety of acclidinium bromide in the treatment of chronic obstructive pulmonary disease have met their primary end point but demonstrated less benefit than anticipated, according to a corporate statement.

The double-blind, placebo-controlled phase III studies "confirm the bronchodilatory effect of acclidinium at the dose tested, although the magnitude was lower than seen in previous studies," according to a statement from Almirall, a Spanish pharmaceutical company.

The company is working to further evaluate the data and determine dosing

alternatives for the novel long-acting inhaled anticholinergic bronchodilator. A dose of 200 mcg acclidinium administered once daily through a dry-powder inhaler was selected for the two phase III studies.

ACCLAIM/COPD was designed to assess acclidinium bromide for the treatment of moderate to severe chronic obstructive pulmonary disease (COPD). The primary end point was trough forced expiratory volume in 1 second. Both ACCLAIM/COPD trials were conducted across 23 countries, with 1,647 COPD patients randomized worldwide. The first was conducted in Europe, the other primarily in North America. ■

This newspaper and "The Pink Sheet" are published by Elsevier.

# Large Study Links Allergic Rhinitis to Adult-Onset Asthma

BY SHARON WORCESTER  
Elsevier Global Medical News

**R**hinitis was a strong predictor of adult-onset asthma, according to findings from an 8-year population-based study in Europe.

In the European Community Respiratory Health Survey, data from 6,461 participants showed that allergic rhinitis was associated with an increased risk of adult-onset asthma (adjusted relative risk of 3.53), as was nonallergic rhinitis, although to a lesser degree (adjusted relative risk of 2.71), Dr. Rafea Shaaban of Bichat Teaching Hospital, Paris, and colleagues reported in the Sept. 20 issue of the *Lancet*.

Participants were aged 20-44 years without asthma at baseline. They were divided into four groups: a control group including 3,163 individuals with no atopy and no rhinitis, an atopy-only group including 704 individuals with atopy but no rhinitis, a nonallergic rhinitis group including 1,377 people with rhinitis but no atopy, and an allergic rhinitis group including 1,217 people with atopy and rhinitis.

A total of 140 individuals developed asthma during the 8.8-year study period, for a cumulative incidence of 2.2%. The incidence in the groups, respectively, was 1.1%, 1.9%, 3.1%, and 4.0%. The differences among the groups were statistically significant, but only allergic rhinitis in those identified by a skin-prick test as having dust mite sensitization was found to be associated with increased risk of asthma independently of other allergens (*Lancet* 2008;372:1049-57).

A possible explanation for the dust mite link, the investigators said, is that patients with allergic rhinitis in response to mites are likely to have nasal symptoms over a longer period of time, because mites are a perennial indoor allergen. That theory is consistent with the findings of at least one other study showing that early exposure to dust mite allergen is associated with an increased risk of childhood asthma.

Sensitization to allergens in addition to mites was associated with additional small increases in asthma risk. For example, in those sensitized to dust mites, sensitization to cats raised asthma risk from 4.6% to 6.4%, and sensitization to grass raised the risk to 7.6%. Sensitization to birch increased the risk to 9.1%, the investigators noted.

Those increases did not reach statistical significance, but that may be because of the small number of patients with those sensitivities, the researchers suggested.

Although prior epidemiological and clinical studies have shown a close relationship between asthma and allergic rhinitis, the nature of the link between the two has remained unclear. The current study, however, provides new evidence that rhinitis is predictive of asthma development, the investigators said, along with support of hypotheses suggesting that rhinitis might be a cause of asthma.

The current findings also suggest bronchial hyperresponsiveness (BHR) is "an intermediate factor in the process leading from allergic rhinitis to asthma," the investigators noted. Not only is allergic rhinitis shown in this and prior studies to be a risk factor for BHR in nonasthmatic adults,

they added, but there is now substantial evidence that asymptomatic BHR frequently precedes—and can be considered a risk factor for—symptomatic asthma.

Because the association between asthma and allergic rhinitis in the current study decreased substantially after controlling for BHR, it is likely that part of the effect of allergic rhinitis on development of asthma is mediated through the development of BHR, the investigators said. "This observation is important, because BHR is thought to be a dynamic process, and can

be decreased by anti-inflammatory therapy," they wrote.

Interventional studies to assess the effects of rhinitis treatment on reducing the incidence of asthma—an effect that has been observed in clinical trials—are necessary to verify this effect, they concluded.

In an editorial that accompanied the study, Dr. Erika von Mutius of University Children's Hospital in Munich noted that "the idea that allergic rhinitis could cause asthma raises the possibility of preventing asthma by preventing atopic

sensitization, which could in turn prevent allergic rhinitis."

The long-term preventive effect that immunotherapy might have is unknown, she added, although it can improve nasal symptom scores, reduce airway responsiveness, and thus cut asthma burden in patients with allergic rhinitis (*Lancet* 2008; 372:1012-14). However, "even if immunotreatments work, the fairly low population-attributable risk might diminish the overall effect of this therapeutic approach," she cautioned. ■

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# Steroids Decreased Resistance to Albuterol Therapy

BY FRAN LOWRY  
Elsevier Global Medical News

Steroids may prevent or reverse the desensitization that occurs with prolonged exposure to short-acting  $\beta_2$ -adrenergic receptor agonists in the treatment of asthma and chronic obstructive pulmonary disease, according to a University of Pennsylvania study.

The findings suggest that combination therapy using a steroid and a short-acting  $\beta_2$ -agonist might offer therapeutic benefit

greater than either therapy alone for the treatment of asthma and chronic obstructive pulmonary disease (COPD), wrote Phillip R. Cooper, Ph.D., and Dr. Reynold A. Panettieri Jr., the study authors.

Their study was released online Sept. 9, 2008, as an article in press by the Journal of Allergy and Clinical Immunology (J. Allergy Clin. Immunol. [doi: 10.1016/j.jaci.2008.07.040]).

The investigators incubated slices of normal lung tissue from humans containing small airways with the short-acting

$\beta_2$ -adrenergic receptor agonist albuterol for periods of 3, 6, or 12 hours at different concentrations. After incubation of the lung tissue slices with carbachol to induce smooth muscle contraction, they found that the albuterol incubation weakened subsequent isoproterenol-induced relaxation in a dose- and time-dependent manner.

After 12 hours of albuterol incubation, the researchers noted a 40% decrease in maximum relaxation and a 45% decrease in airway sensitivity, compared with control

values. The differences were statistically significant. In contrast, preincubating the slices of lung tissue with dexamethasone for 1 hour prevented the albuterol-induced desensitization. However, a shorter (30-minute) dexamethasone incubation didn't change albuterol-induced desensitization, according to the investigators.

The authors noted that their study is the first to demonstrate a model of  $\beta_2$ -adrenergic receptor tolerance in normal human small airways. That is important, they wrote, because previous research in this area has attempted to study the mechanisms of inducing  $\beta$ -agonist tolerance in animal models and single-cell preparations, which has made translating the findings to human lung tissue very difficult.

"The great thing about this work is that we are actually using small airways, which is the part of the lung that has the airway obstruction in asthma and COPD," Dr. Cooper said in an interview. "So we were looking specifically at the correct part of the lung."

The study provides a platform to determine the exact mechanisms of  $\beta$ -agonist desensitization in human small airways, as well as ways of preventing tolerance to those agonists in human airway disease, the investigators wrote.

For now, they noted, the important take-home message is that steroids potentially can reverse that tolerance. "Our work promotes combination therapy—supplying patients with a steroid and a  $\beta$ -agonist together," Dr. Cooper said.

The authors declared they had no conflicts of interest.

**Dr. Susan Harding, FCCP, comments:** This *in vitro* study gives us potential translational information that is useful. Although the bronchoconstriction was induced by carbachol, a cholinergic agonist, and combined simultaneous incubation with dexamethasone and albuterol was not reported, this study supports the concept that combined use of corticosteroids with short-acting  $\beta_2$ -agonists may avert resistance to SABAs.

## FDA Site Lists Drugs With Safety Issues

The Food and Drug Administration has posted on its Web site its first quarterly report that lists certain drugs being evaluated for potential safety issues. The drugs in the report, "Potential Signals of Serious Risks/New Safety Information," have been identified by FDA reviewers based on reports from the FDA's Adverse Event Reporting System (AERS) database. To view the report, visit [www.fda.gov/cder/aers/potential\\_signals/potential\\_signals\\_2008Q1.htm](http://www.fda.gov/cder/aers/potential_signals/potential_signals_2008Q1.htm).



The important take-home message is that steroids potentially can reverse that tolerance.  
DR. COOPER

### BRIEF SUMMARY

Please see package insert for full prescribing information.

**Azactam**<sup>®</sup>  
aztreonam IV/IM 1g/2g

**INDICATIONS AND USAGE:** To reduce the development of drug-resistant bacteria and maintain the effectiveness of AZACTAM<sup>®</sup> (aztreonam for injection, USP) and other antibacterial drugs, AZACTAM should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. Before initiating treatment with AZACTAM, appropriate specimens should be obtained for isolation of the causative organism(s) and for determination of susceptibility to aztreonam. Treatment with AZACTAM may be started empirically before results of the susceptibility testing are available; subsequently, appropriate antibiotic therapy should be continued.

AZACTAM is indicated for the treatment of the following infections caused by susceptible gram-negative microorganisms:

**Urinary Tract Infections** (complicated and uncomplicated), including pyelonephritis and cystitis (initial and recurrent) caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Klebsiella oxytoca*, *Citrobacter* species\* and *Serratia marcescens*.\*

**Lower Respiratory Tract Infections**, including pneumonia and bronchitis caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Proteus mirabilis*, *Enterobacter* species and *Serratia marcescens*.\*

**Septicemia** caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus mirabilis*,\* *Serratia marcescens*\* and *Enterobacter* species.

**Skin and Skin-Structure Infections**, including those associated with postoperative wounds, ulcers and burns caused by *Escherichia coli*, *Proteus mirabilis*, *Serratia marcescens*, *Enterobacter* species, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Citrobacter* species.\*

**Intra-abdominal Infections**, including peritonitis caused by *Escherichia coli*, *Klebsiella* species including *K. pneumoniae*, *Enterobacter* species including *E. cloacae*,\* *Pseudomonas aeruginosa*, *Citrobacter* species\* including *C. freundii*\* and *Serratia* species\* including *S. marcescens*.\*

**Gynecologic Infections**, including endometritis and pelvic cellulitis caused by *Escherichia coli*, *Klebsiella pneumoniae*,\* *Enterobacter* species\* including *E. cloacae*\* and *Proteus mirabilis*.\*

AZACTAM is indicated for adjunctive therapy to surgery in the management of infections caused by susceptible organisms, including abscesses, infections complicating hollow viscus perforations, cutaneous infections and infections of serous surfaces. AZACTAM is effective against most of the commonly encountered gram-negative aerobic pathogens seen in general surgery.

**Concurrent Therapy:** Concurrent initial therapy with other antimicrobial agents and AZACTAM is recommended before the causative organism(s) is known in seriously ill patients who are also at risk of having an infection due to gram-positive aerobic pathogens. If anaerobic organisms are also suspected as etiologic agents, therapy should be initiated using an anti-anaerobic agent concurrently with AZACTAM (see **DOSE AND ADMINISTRATION**). Certain antibiotics (e.g., cefoxitin, imipenem) may induce high levels of beta-lactamase *in vitro* in some gram-negative aerobes such as *Enterobacter* and *Pseudomonas* species, resulting in antagonism to many beta-lactam antibiotics including aztreonam. These *in vitro* findings suggest that such beta-lactamase inducing antibiotics not be used concurrently with aztreonam. Following identification and susceptibility testing of the causative organism(s), appropriate antibiotic therapy should be continued.

**CONTRAINDICATIONS:** This preparation is contraindicated in patients with known hypersensitivity to aztreonam or any other component in the formulation.

**WARNINGS:** Both animal and human data suggest that AZACTAM is rarely cross-reactive with other beta-lactam antibiotics and weakly immunogenic. Treatment with aztreonam can result in hypersensitivity reactions in patients with or without prior exposure. (See **CONTRAINDICATIONS**.)

Careful inquiry should be made to determine whether the patient has any history of hypersensitivity reactions to any allergens.

While cross-reactivity of aztreonam with other beta-lactam antibiotics is rare, this drug should be administered with caution to any patient with a history of hypersensitivity to beta-lactams (e.g., penicillins, cephalosporins, and/or carbapenems). Treatment with aztreonam can result in hypersensitivity reactions in patients with or without prior exposure to aztreonam. If an allergic reaction to aztreonam occurs, discontinue the drug and institute supportive treatment as appropriate (e.g., maintenance of ventilation, pressor amines, antihistamines, corticosteroids). Serious hypersensitivity reactions may require epinephrine and other emergency measures. (See **ADVERSE REACTIONS**.)

*Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including AZACTAM and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*. *C. difficile* produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Rare cases of toxic epidermal necrolysis have been reported in association with aztreonam in patients undergoing bone marrow transplant with multiple risk factors including sepsis, radiation therapy and other concomitantly administered drugs associated with toxic epidermal necrolysis.

**PRECAUTIONS: General:** In patients with impaired hepatic or renal function, appropriate monitoring is recommended during therapy.

If an aminoglycoside is used concurrently with aztreonam, especially if high dosages of the former are used or if therapy is prolonged, renal function should be monitored because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics.

The use of antibiotics may promote the overgrowth of nonsusceptible organisms, including gram-positive organisms (*Staphylococcus aureus* and *Streptococcus faecalis*) and fungi. Should superinfection occur during therapy, appropriate measures should be taken.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Carcinogenicity studies in animals have not been performed.

Genetic toxicology studies performed *in vivo* and *in vitro* with aztreonam in several standard laboratory models revealed no evidence of mutagenic potential at the chromosomal or gene level.

Two-generation reproduction studies in rats at daily doses up to 20 times the maximum recommended human dose, prior to and during gestation and lactation, revealed no evidence of impaired fertility. There was a slightly reduced survival rate during the lactation period in the offspring of rats that received the highest dosage, but not in offspring of rats that received five times the maximum recommended human dose.

**Pregnancy: Pregnancy Category B:** Aztreonam crosses the placenta and enters the fetal circulation.

Studies in pregnant rats and rabbits, with daily doses up to 15 and 5 times, respectively, the maximum recommended human dose, revealed no evidence of embryo- or fetotoxicity or teratogenicity. No drug induced changes were seen in any of the maternal, fetal, or neonatal parameters that were monitored in rats receiving 15 times the maximum recommended human dose of aztreonam during late gestation and lactation.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, aztreonam should be used during pregnancy only if clearly needed.

**Nursing Mothers:** Aztreonam is excreted in human milk in concentrations that are less than 1 percent of concentrations determined in simultaneously obtained maternal serum; consideration should be given to temporary discontinuation of nursing and use of formula feedings.

**Pediatric Use:** The safety and effectiveness of intravenous AZACTAM (aztreonam for injection, USP) have been established in the age groups 9 months to 16 years. Use of AZACTAM in these age groups is supported by evidence from adequate and well-controlled studies of AZACTAM in adults with additional efficacy, safety, and pharmacokinetic data from non-comparative clinical studies in pediatric patients. Sufficient data are not available for pediatric patients under 9 months of age or for the following treatment indications/pathogens: septicemia and skin and skin-structure infections (where the skin infection is believed or known to be due to *H. influenzae* type b). In pediatric patients with cystic fibrosis, higher doses of AZACTAM may be warranted. (See **CLINICAL PHARMACOLOGY, DOSAGE AND ADMINISTRATION**, and **CLINICAL STUDIES**.)

**Geriatric Use:** Clinical studies of AZACTAM did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.<sup>10</sup> In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Because elderly patients are more likely to have decreased renal function, renal function should be monitored and dosage adjustments made accordingly (see **DOSE AND ADMINISTRATION: Renal Impairment in Adult Patients and Dosage in the Elderly**).

**ADVERSE REACTIONS:** Local reactions such as phlebitis/thrombophlebitis following IV administration, and discomfort/swelling at the injection site following IM administration occurred at rates of approximately 1.9 percent and 2.4 percent, respectively.

Systemic reactions (considered to be related to therapy or of uncertain etiology) occurring at an incidence of 1 to 1.3 percent included diarrhea, nausea and/or vomiting, and rash. Reactions occurring at an incidence of less than 1 percent are listed within each body system in order of decreasing severity:

**Hypersensitivity**—anaphylaxis, angioedema, bronchospasm  
**Hematologic**—pancytopenia, neutropenia, thrombocytopenia, anemia, eosinophilia, leukocytosis, thrombocytosis

**Gastrointestinal**—abdominal cramps; rare cases of *C. difficile*-associated diarrhea, including pseudomembranous colitis, or gastrointestinal bleeding have been reported. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment. (See **WARNINGS**.)

**Dermatologic**—toxic epidermal necrolysis (see **WARNINGS**), purpura, erythema multiforme, exfoliative dermatitis, urticaria, petechiae, pruritus, diaphoresis

**Cardiovascular**—hypotension, transient ECG changes (ventricular bigeminy and PVC), flushing  
**Respiratory**—wheezing, dyspnea, chest pain

**Hepatobiliary**—hepatitis, jaundice

**Nervous System**—seizure, confusion, vertigo, paresthesia, insomnia, dizziness

**Musculoskeletal**—muscular aches

**Special Senses**—tinnitus, diplopia, mouth ulcer, altered taste, numb tongue, sneezing, nasal congestion, halitosis

**Other**—vaginal candidiasis, vaginitis, breast tenderness

**Body as a Whole**—weakness, headache, fever, malaise

**Pediatric Adverse Reactions:** Of the 612 pediatric patients who were treated with AZACTAM in clinical trials, less than 1% required discontinuation of therapy due to adverse events. The following systemic adverse events, regardless of drug relationship, occurred in at least 1% of treated patients in domestic clinical trials: rash (4.3%), diarrhea (1.4%), and fever (1.0%). These adverse events were comparable to those observed in adult clinical trials.

In 343 pediatric patients receiving intravenous therapy, the following local reactions were noted: pain (12%), erythema (2.9%), induration (0.9%), and phlebitis (2.1%). In the US patient population, pain occurred in 1.5% of patients, while each of the remaining three local reactions had an incidence of 0.5%.

The following laboratory adverse events, regardless of drug relationship, occurred in at least 1% of treated patients: increased eosinophils (6.3%), increased platelets (3.6%), neutropenia (3.2%), increased AST (3.8%), increased ALT (6.5%), and increased serum creatinine (5.8%).

In US pediatric clinical trials, neutropenia (absolute neutrophil count less than 1000/mm<sup>3</sup>) occurred in 11.3% of patients (8/71) younger than 2 years receiving 30 mg/kg q6h. AST and ALT elevations to greater than 3 times the upper limit of normal were noted in 15–20% of patients aged 2 years or above receiving 50 mg/kg q6h. The increased frequency of these reported laboratory adverse events may be due to either increased severity of illness treated or higher doses of AZACTAM administered.

**Adverse Laboratory Changes:** Adverse laboratory changes without regard to drug relationship that were reported during clinical trials were:

**Hepatic**—elevations of AST (SGOT), ALT (SGPT), and alkaline phosphatase; signs or symptoms of hepatobiliary dysfunction occurred in less than 1 percent of recipients (see above).

**Hematologic**—increases in prothrombin and partial thromboplastin times, positive Coombs' test.

**Renal**—increases in serum creatinine.

**OVERDOSAGE:** If necessary, aztreonam may be cleared from the serum by hemodialysis and/or peritoneal dialysis.

\*Efficacy for this organism in this organ system was studied in fewer than ten infections.

AZACTAM is a trademark of Elan Pharmaceuticals, Inc.

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Bristol-Myers Squibb Company  
Princeton, NJ 08543 U.S.A.

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# Genetic Screening Boosted Survival in Metastatic NSCLC

*Patients selected by genotype for erlotinib treatment achieved 22-month median survival.*

BY JANE SALODOF MACNEIL  
Elsevier Global Medical News

STOCKHOLM — Screening for mutations in the epidermal growth factor receptor gene enabled investigators from the Spanish Lung Cancer Group to achieve significant survival gains by selecting patients most likely to benefit from the drug erlotinib.

“For the first time in lung cancer we have a useful predictive marker,” Dr. Rafael Rossell, the principal investigator of the study, said during a press briefing at the European Society for Medical Oncology Congress.

Dr. Rossell presented data on the first 191 of more than 300 patients in a prospective study of customized treatment for lung cancer.

Median survival reached 22 months for patients with metastatic non-small cell lung cancer (NSCLC) who had exon 19 or 21 mutations. The time to progression was 12 months for these patients, and 71% had

a response to erlotinib (Tarceva), a tyrosine kinase inhibitor of the epidermal growth factor receptor (EGFR).

Even better results were achieved in subgroups of patients who had a performance status of 0, were women, or did not have brain metastases. Those whose performance status was measured as 0 had yet to reach median survival, he said.

In contrast, only 30% of patients with metastatic NSCLC typically respond to chemotherapy in cancer studies, according to Dr. Rossell. Their time to progression is just 5 months, and their median survival only half as long at 11 months.

“There is no excuse not to test for these mutations,” said Dr. Rossell, chief of the medical oncology service and scientific director of oncology research at the Catalan Institute of Oncology, Hospital German Trias I Pujol in Barcelona.

“Testing is the first step toward a dramatic improvement in subgroups of patients,” he said.

For the study, investigators screened

tumor samples of 2,294 patients from 130 hospitals in Spain, Argentina, Colombia, Mexico, the United States, the United Kingdom, and Italy from April 2005 to July 2008.

Only patients whose tumor specimens showed a deletion in exon 19 of EGFR’s tyrosine kinase domain or mutation in exon 21 were selected for treatment with erlotinib.

EGFR assessment was performed at a central laboratory and results were delivered in 8 days, Dr. Rossell said. Such testing is widely available, he added. Some patients have inadequate tumor specimen, but testing circulating DNA in serum is an option.

EGFR mutations were discovered in 2004, he noted, and have previously been shown to occur primarily in small subgroups of lung cancer patients: women, never smokers, and Asians.

In the new study, he reported that 30.3% of women but only 8.3% of men harbored a mutation ( $P$  less than .0001). Women with exon 19 deletions also appeared to benefit more, with a median survival of 28 months when erlotinib was given, compared with 23 months for men. This dif-

ference was not statistically significant, however ( $P = .08$ ).

Mutations were found in 38.4% of never smokers, but only 9.2% of former smokers, and just 6.1% of current smokers, differences that were also highly statistically significant ( $P$  less than .0001).

Stratification by histology showed that mutations occurred in 17.3% of patients with adenocarcinoma, 23.7% of those with bronchioloalveolar carcinoma, 11.9% of large-cell anaplastic lung cancers, and 6.3% of those classified as others ( $P$  less than .0002).

Despite the relatively small proportion of the lung cancer population that stands to benefit from erlotinib, Dr. Rossell emphasized that the improved survival is sufficiently great to make testing worthwhile. The benefits achieved in the trial are “a new landmark in lung cancer,” he said.

To further illuminate “the prognostic and predictive relevance of EGFR mutations,” the Spanish Lung Cancer Group has started a phase III study, the European Randomized Trial of Tarceva vs. Chemotherapy (EURTAC) for stage IV NSCLC. ■

## Tiotropium Didn’t Change Rate of FEV<sub>1</sub> Decline in COPD

BY PATRICE WENDLING  
Elsevier Global Medical News

Regular use of the inhaled anticholinergic tiotropium did not significantly reduce the rate of decline in mean forced expiratory volume in 1 second in patients with chronic obstructive pulmonary disease, a large randomized, double-blind trial has shown.

However, tiotropium was associated with improvements in the secondary end points, including lung function, quality of life, and exacerbation rate, according to the study published online Oct. 5 in the *New England Journal of Medicine* (N. Engl. J. Med. 2008;359:1543-54).

The trial, known as UPLIFT (Understanding Potential Long-Term Impacts on Function with Tiotropium), randomized 5,993 patients at 490 centers in 37 countries to 4 years of therapy with either tiotropium 18 mcg inhaled once daily or placebo. They were allowed to use other respiratory medications, except inhaled anticholinergics. Patients (mean age 66 years) had moderate to very severe COPD and a mean baseline forced expiratory volume in 1 second (FEV<sub>1</sub>) of 1.32 L after bronchodilation (48% of predicted value).

There were no significant differences between the treatment and placebo groups in the rate of decline in the mean values for FEV<sub>1</sub> and forced vital capacity (FVC) either before or after

bronchodilation from day 30 to the end of study, lead study author Dr. Donald P. Tashkin of the University of California, Los Angeles, and his associates reported. The annual rate of decline was 30 mL/yr in both groups before bronchodilation, and 40 mL in the tiotropium group and 42 mL in the placebo group after bronchodilation.

Mean absolute improvements in FEV<sub>1</sub> in the tiotropium group, compared with the placebo group, were maintained at all time points after randomization, and ranged from 87 mL to 103 mL before bronchodilation and from 47 mL to 65 mL after bronchodilation. The differences were statistically significant.

The incidence of most serious adverse events was lower in the tiotropium group than in the placebo group, including a reduced risk of congestive heart failure, COPD exacerbation, dyspnea, and respiratory failure, the authors wrote. In addition, the incidence rate for myocardial infarction was 0.69/100 patient-years for tiotropium, compared with 0.97/100 patient-years for placebo (relative risk, 0.71).

The incidence rate of cardiac failure, however, was 0.61/100 patient-years for tiotropium, compared with 0.48/100 patient-years for placebo (RR, 1.25).

Those findings are noteworthy, as a recently published meta-analysis showed that the use of either inhaled tiotropium or ipratropium significantly increased

the risk of cardiovascular death, MI, or stroke by about 58% among patients with COPD (JAMA 2008;300:1439-50) (see story, p. 1). Pfizer Inc. and Boehringer Ingelheim GmbH, which comarket inhaled tiotropium under the trade name Spiriva and funded the UPLIFT trial, strongly rejected those findings.

The yearly rate of decline in FEV<sub>1</sub> observed in UPLIFT was lower than rates reported in other prospective interventional trials, Dr. Tashkin and associates noted, including EUROSCOP (European Respiratory Society Study on Chronic Obstructive Pulmonary Disease) and ISOLDE (Inhaled Steroids in Obstructive Lung Disease in Europe).

Potential explanations for the discrepancies are that UPLIFT allowed for prescription of all respiratory therapies at the discretion of the physicians. In addition, only 30% of patients were current smokers at baseline, compared with 38%-90% in other studies. The UPLIFT investigators also cited differences in study design, patient selection, and regional factors.

The trial’s failure to find a difference in the rates of decline in FEV<sub>1</sub> might have been predictable, given previous trials’ results and the fact that smoking cessation is the only intervention that meets the criteria of disease-modifying therapy, said Dr. John J. Reilly of the University of Pittsburgh in an accompanying editorial (N. Engl. J. Med. 2008;359:1616-8).

However, Dr. Reilly argued that the issue with UPLIFT and other recent large trials may be a signal-to-noise problem.

“In our efforts to simplify and clarify our definition of COPD, we have promulgated an inclusive definition that relies primarily on spirometric measures to establish the diagnosis,” Dr. Reilly wrote. “There is increasing recognition that FEV<sub>1</sub> alone, while important, does not capture and communicate the heterogeneity of COPD.”

He supported ongoing attempts to define subgroups of patients with COPD to ensure that therapies that are effective in one subgroup will not be discarded because of results of studies that included patients with various

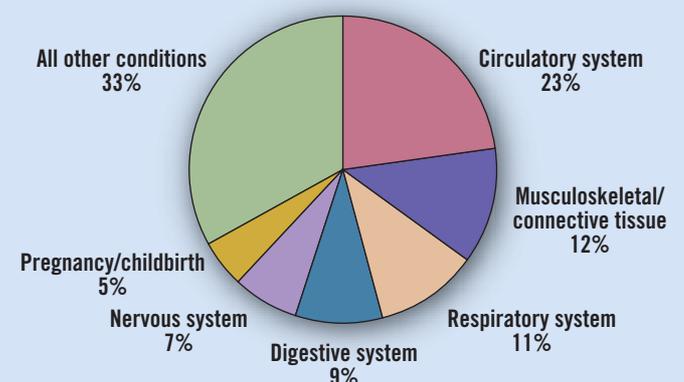
types of COPD. “Although the characteristics that will define these subgroups remain to be determined... it is clear that the use of FEV<sub>1</sub> alone is not sufficient,” Dr. Reilly wrote.

Dr. Tashkin disclosed receiving consulting fees from AstraZeneca, Boehringer Ingelheim, Dey Laboratories, and Schering; lecture fees from AstraZeneca, Boehringer Ingelheim, and Dey Laboratories; and grant support from Almirall, AstraZeneca, Boehringer Ingelheim, Dey Laboratories, GlaxoSmithKline, Ivax, MediciNova, Nabi Biopharmaceuticals, Novartis, Pfizer, and Sepracor.

Dr. Reilly reported receiving consulting fees from Indevus Pharmaceuticals and research support from Aeris Therapeutics. ■

### DATA WATCH

#### Respiratory Conditions Accounted for 11% of Hospital Costs in 2006



Note: Based on data from the Healthcare Cost and Utilization Project. Source: Agency for Healthcare Research and Quality

# FOR PREVENTION OF RECURRENT MPE

## SCLEROSOL® INTRAPLEURAL AEROSOL

### Exclusive Features:

#### FDA APPROVED

- Gamma Irradiated • Single Use, 4 gram Dosage • 2 1/2-Year Shelf Life
- Packaged in a Sterile Pouch with Two Delivery Tubes (15 cm & 25 cm)

Sclerosol® Intrapleural Aerosol is indicated for the prevention of recurrent MPE in symptomatic patients. A cost-effective treatment for MPE, Sclerosol provides uniform, consistent, rapid, and clean administration.



#### DESCRIPTION

Sclerosol® Intrapleural Aerosol (sterile talc powder 4 g) is a sclerosing agent for intrapleural administration supplied as a single-use, pressurized spray canister with two delivery tubes of 15 cm and 25 cm in length. Each canister contains 4 g of talc, either white or off-white to light grey, asbestos-free, and brucite-free grade of talc of controlled granulometry. The composition of the talc is ≥ 95% talc as hydrated magnesium silicate. The empirical formula is Mg<sub>3</sub>Si<sub>4</sub>O<sub>10</sub>(OH)<sub>2</sub> with molecular weight of 379.3. Associated naturally occurring minerals include chlorite (hydrated aluminum and magnesium silicate), dolomite (calcium and magnesium carbonate), calcite (calcium carbonate) and quartz. Talc is practically insoluble in water, and in dilute solutions of acids and alkali hydroxides. The canister and delivery tubes have been sterilized by gamma irradiation. The aerosol propellant contained in Sclerosol® Intrapleural Aerosol is dichlorodifluoromethane (CFC-12) with 26 g present per canister. The canister delivers 0.4 g of talc per second through the valve and the product contains no other excipients.

#### INDICATIONS AND USAGE

Sclerosol® Intrapleural Aerosol, administered by aerosol during thoracoscopy or open thoracotomy, is indicated to prevent recurrence of malignant pleural effusions in symptomatic patients.

#### CONTRAINDICATIONS

None known.

#### WARNINGS

None.

#### PRECAUTIONS

##### General:

**1) Future procedures.** The possibility of future diagnostic and therapeutic procedures involving the hemithorax to be treated must be considered prior to administering Sclerosol® Intrapleural Aerosol. Sclerosis of the pleural space may preclude subsequent diagnostic procedures of the pleura on the treated side. Talc sclerosis may complicate or preclude future ipsilateral lung resective surgery, including pneumonectomy for transplantation purposes.

**2) Use in potentially curable disease.** Talc has no known antineoplastic activity and should not be used for potentially curable malignancies where systemic therapy would be more appropriate, e.g., a malignant effusion secondary to a potentially curable lymphoma.

**3) Potential pulmonary complications.** Acute pneumonitis or acute respiratory distress syndrome (ARDS) have rarely been reported in association with intrapleural talc administration. Whether these were causally related to talc is unclear. In none of the reported cases was talc applied thoracoscopically or by insufflation. Three of four case reports of ARDS have occurred after treatment with 10 g of talc administered via intrapleural chest tube instillation. One patient died one month post treatment and two patients recovered without further sequelae.

Intravenous administration of talc is a well-recognized cause of pulmonary hypertension and pulmonary lung parenchymal disease, but these complications have not been reported after intrapleural administration. Pulmonary diseases, e.g., silicosis or asbestosis-like diseases, chronic bronchitis, bronchogenic carcinoma, and pleural plaques have been reported in association with inhaled talc.

**4) Contents under pressure.** The contents of the Sclerosol® Intrapleural Aerosol (sterile talc powder) canister are under pressure. The canister must not be punctured and should not be used or stored near heat or open flame.

**Drug Interactions:** It is not known whether the effectiveness of a second sclerosing agent after prior talc pleurodesis would be diminished by the absorptive properties of talc.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Studies on the carcinogenicity of talc have been performed using non-standard designs, which prevent firm conclusions on its carcinogenicity. With single intraperitoneal administration to mice at 20 mg and observation for at least 6 months, or 4 weekly doses administered intraperitoneally at 25 mg/dose to rats with observation for at least 84 weeks, tumor incidence was not increased. In these studies, the talc and its asbestos content were not characterized. Genotoxicity was assessed in cultures of rat pleural mesothelial cells (RPMC), as unscheduled DNA syntheses (UDS) and sister chromatid exchanges (SCEs). None of the talc samples (which were asbestos free) enhanced UDS or SCEs in treated cultures. No information is available on impairment of fertility in animals by talc.

**Pregnancy:** Pregnancy category B. An oral administration study has been performed in the rabbit at 900 mg/kg, approximately 5-fold higher than the human dose on mg/m<sup>2</sup> basis, and has revealed no evidence of teratogenicity due to talc. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should not be used during pregnancy unless it is clearly needed.

**Pediatric Use:** The safety and efficacy of Sclerosol® Intrapleural Aerosol (sterile talc powder) in pediatric patients has not been established.

**Geriatric Use:** The mean and median ages of patients treated with talc in the clinical studies table were 50-62 years. No analyses to specifically evaluate the safety and efficacy in the geriatric population have been reported.

#### ADVERSE REACTIONS

Talc administration has been described in more than 1500 patients reported in the medical literature. Patients with malignant pleural effusions were treated with talc via poudrage or slurry. In general, with respect to reported adverse experiences, it is difficult to distinguish the effects of talc from the effects of the procedure(s) associated with its administration. The most reported common adverse experiences were fever and pain. Almost all of the cases of fever, and over half of the cases of pain, were in patients who received diagnostic biopsies at the time of talc administration.

**Infections:** Empyema was a rare complication of talc administration and/or the procedure. Biopsies had been obtained prior to onset in over half the reported cases.

**Respiratory:** Rare instances of pneumonia, ARDS, dyspnea, bronchopleural fistula, hemoptysis, and pulmonary emboli have been reported.

**Cardiovascular:** Tachycardia, myocardial infarction, hypotension, hypovolemia, and asystolic arrest associated with surgery and/or anesthesia have been rarely reported.

**Delivery Procedure:** Adverse reactions due to the delivery procedure and the chest tube may include: infection at the site of thoracostomy or thoracoscopy, localized bleeding, and subcutaneous emphysema.

**Chronic Toxicity:** Lange et al. (Thorax 1988;43:559) reported on 114 consecutive cases of idiopathic spontaneous pneumothorax treated with talc poudrage (60 patients), or simple drainage (54 patients) via an intercostal tube. Pulmonary function tests (FEV<sub>1</sub>, VC, TLC, and RV) 22 to 35 years after treatment, showed no significant differences in the incidence of pleural changes between the two groups. Two patients treated with talc poudrage had more extensive pleural thickening with calcification. The mean total lung capacities were 89% of predicted in the talc group and 96% in the drainage only group. Fourteen patients (12 lifelong heavy smokers, 2 non-smokers) had airflow limitation (5 severe). Source and purity of the talc used was not reported. No cases of mesothelioma were reported. One case report noted the occurrence of adenocarcinoma of the chest wall two years after pleurodesis following 10 g of 1% iodized talc (administered for recurrent pneumothorax).

#### OVERDOSAGE

Overdosages have not been reported. (See PRECAUTIONS: 3) Potential pulmonary complications.

#### DOSAGE AND ADMINISTRATION

Sclerosol® Intrapleural Aerosol (sterile talc powder) is administered after adequate drainage of the effusion. It has been suggested that success of the pleurodesis is related to the completeness of the drainage of the pleural fluid, as well as full reexpansion of the lung, both of which will promote symphysis of the pleural surfaces.

The usual dosage of Sclerosol® Intrapleural Aerosol (sterile talc powder) is a single 4-8 g dose delivered intrapleurally from the spray canister (1-2 cans), which delivers talc at a rate of 0.4 g per second.

#### ADMINISTRATION PROCEDURE

Shake canister well before usage. Remove protective cap and securely attach actuator button with its delivery tube (either 15 cm or 25 cm) to the valve stem of canister.

Insert delivery tube through pleural trocar, taking care not to place the distal end of the delivery tube adjacent to the lung parenchyma or directly against the chest wall. While firmly holding the delivery tube and pleural trocar together in one hand, gently apply pressure to the actuator button on the canister. Sclerosol® Intrapleural Aerosol is not delivered by metered dose, but depends on the extent and duration of manual compression of the actuator button on the canister. The distal end of the delivery tube should be pointed in several different directions, while short bursts are administered in order to distribute the talc powder equally and extensively on all visceral and parietal pleural surfaces. For optimal distribution, always maintain the Sclerosol® Intrapleural Aerosol (sterile talc powder) canister in the upright position. After application, discard the canister and delivery tube. The duration of chest tube drainage following talc sclerosis is dictated by the clinical situation.

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## Third-Trimester Flu Vaccine Protected Infants

BY ROBERT FINN  
Elsevier Global Medical News

HONOLULU — When women are given influenza vaccine in their third trimester of pregnancy, their infants receive protection against flu infection, results of a randomized controlled trial of more than 300 pregnant women confirm.

“This is the first randomized controlled trial of maternal immunization with influenza vaccine,” Dr. Mark C. Steinhoff reported at the annual meeting of the Pediatric Academic Societies. “Although [maternal immunization] is a U.S. government policy, it’s one of the few not based on randomized controlled trials.”

The Centers for Disease Control and Prevention guideline states. “Vaccination with inactivated influenza vaccine is recommended for the following persons who are at increased risk for severe complications from influenza: ... Women who will be pregnant during the influenza season (MMWR 2006;55[No. RR-10]:11-2).”

The study was part of the Maternal Gift Study, which involved 340 pregnant women and 331 live births in a middle-class urban population in Bangladesh. Women in the study were randomized to receive either influenza vaccine or pneumococcal conjugate vaccine during their third trimester of pregnancy. For the purposes of this analysis, the investigators used the mother-infant pairs receiving pneumococcal vaccine as the control group.

The mothers were an average 25 years old, and were vaccinated an average 55 days before giving birth. Ninety-two percent gave birth in a hospital or clinic, 46% by cesarean delivery. The infants averaged just above 3 kg at birth and were breast-fed exclusively an average of 14 weeks.

The investigators looked both at proven influenza illness and at all febrile respiratory illnesses as outcome measures. The trivalent influenza vaccine was associated with a 63% reduction in proven influenza in infants 0-6 months of age and a 30% reduction in all febrile respiratory illnesses in infants and their mothers.

The fact that the influenza vaccine was compared with the pneumococcal vaccine and not with placebo probably resulted in an underestimate of the influenza vaccine’s effectiveness, said Dr. Steinhoff of Johns Hopkins University, Baltimore. “It’s possible that pneumococcal vaccine could reduce some of the viral illnesses.”

Furthermore, the vaccine’s protective effect appeared to last at least until the infants were 5 months old. This is particularly important because current U.S. guidelines do not recommend influenza vaccine for children younger than 6 months old.

Dr. Steinhoff disclosed that he has served on Sanofi’s speakers bureau and has received research support from Sanofi-Aventis, Wyeth, and Merck & Co. “None of these interactions had any bearing on this particular study,” he said. ■

# Airway Responsiveness More Severe in Asthmatic Girls

BY DOUG BRUNK  
Elsevier Global Medical News

**A**irway responsiveness is more severe in postpubertal females with asthma, compared with their male counterparts, according to results from a large novel study.

The reason for the association is not clear, but it may have to do with hormonal regulation of airway responsiveness, study investigators reported in the Aug. 15 issue of the American Journal of Respiratory and Critical Care Medicine.

"In females with asthma, studies have demonstrated an impaired ability to increase  $\beta_2$ -adrenergic receptor numbers despite a significant increase in airway responsiveness accompanying the luteal phase of the menstrual cycle," Dr. Kelan G. Tantisira and colleagues said.

"This increase in airway responsiveness may be related to relative reductions in

boys became increasingly tolerant to increasing methacholine doses, which suggests a possible decrease in disease severity.

By age 16, more than twice as much methacholine was needed to provoke a 20% constriction in the airways of boys, compared with girls. By age 18, only 15% of girls did not demonstrate any significant degree of airway responsiveness, compared with 27% of boys.

"While our results were not expected, they do point to intriguing mechanisms," Dr. Tantisira of Brigham and Women's

Hospital and Harvard Medical School, both in Boston, said in a prepared statement. "Especially intriguing is that the differences in gender begin at the time of transition into early puberty."

The researchers acknowledged the study had limitations, including that the study "involved a cohort that followed a clinical trial period, making treatment assignment during the trial a potential confounder."

In an accompanying editorial, Dr. Jorrit Gerritsen of Beatrix Children's Hospital and the University of Groningen (the

Netherlands), recommended that the study participants "be followed for as long as possible since these individuals offer a unique opportunity that may provide insight into the natural course of asthma both in male and female subjects" (*Am. J. Respir. Crit. Care Med.* 2008;178:321-4).

The National Heart, Lung, and Blood Institute, and the National Center for Research Resources supported the study. Two of the study researchers disclosed ties to pharmaceutical companies that manufacture asthma medications. ■



The effect may have to do with hormonal regulation of airway responsiveness.

serum estrogen or relative excesses in progesterone," which begins as early as Tanner stage II, the investigators reported.

In addition, they continued, studies conducted in animal models have shown that testosterone "can relax previously contracted airway smooth muscle in what appears to be a nitric oxide mediated mechanism. "Therefore, it is possible that the postpubertal decreases in airway responsiveness that occur among males may be mediated through increases in testosterone levels."

The researchers prospectively evaluated 1,041 children (aged 5-12 years) who had mild to moderate asthma and who were enrolled in CAMP (Childhood Asthma Management Continuation Program).

The mean follow-up was 8.6 years, and participants were administered yearly methacholine challenges to determine the provocative concentration necessary to produce a 20% decrease in forced expiratory volume in 1 second (*Am. J. Respir. Crit. Care Med.* 2008;178:325-31).

Over the course of the follow-up period, each study participant had undergone eight to nine methacholine challenges. The researchers found that the amount of methacholine that was required to provoke airway constriction did not change markedly in girls over that time period. However,

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## Sleep Apnea Linked to BP Nondipping

BY DAMIAN McNAMARA  
Elsevier Global Medical News

People with sleep-disordered breathing were less likely to experience a normal nighttime decrease in systolic blood pressure, and they were at increased risk of adverse cardiac and other outcomes, according to a new prospective study.

Most people experience a 10%-20% dip in their blood pressure at nighttime (Hypertension 1995;26:60-9). Previously, cross-sectional studies showed an association between sleep apnea syndrome and a failure to experience that nighttime decrease in blood pressure (Am. J. Hypertens. 2001;14:887-92; Chest 2002;122:1148-55).

The new study's findings are important because "nocturnal nondipping" associated with sleep-disordered breathing (SDB) has been linked to target organ damage and a poor cardiovascular prognosis (Can. J. Cardiol. 2007;23:132-8; JAMA 1999;282:539-46).

Dr. Khin Mae Hla and her associates assessed 328 adults in the

ongoing Wisconsin Sleep Cohort Study. All participants had a baseline polysomnography study and at least two 24-hour ambulatory blood pressure monitoring assessments during an average 7.2 years of follow-up. Dr. Hla and her colleagues of the departments of medicine and population health sciences at the University of Wisconsin, Madison, reported their findings in *Sleep* (2008;31:795-800).

A total of 18% of participants developed systolic nondipping, and 11% developed diastolic nondipping. Although the researchers did not find an association between SDB and diastolic nondipping, the longitudinal association with systolic BP alterations was significant.

"This failure to experience normal dipping adds to the amassing evidence that sleep-disordered breathing has a causal role in cardiovascular disease, possibly via multiple pathways [JAMA 2003;290:1906-14; J. Clin. Sleep Med. 2007;3:409-15]," the researchers wrote.

The chances of developing systolic nondipping were significantly correlated with baseline severity of SDB in a dose-response fashion.

Mean patient age was 49 years, 63% were men, and the mean body mass index was 29 kg/m<sup>2</sup>. Dr. Hla and her associates controlled for possible confounders, including age, gender, body mass index, smoking, and alcohol use. Use of continuous positive airway pressure (CPAP) by 11 patients, antihypertensive medication use by 42 patients, and inclusion of 8 patients with a history of cardiovascular disease did not significantly alter the findings.

Patients using CPAP were included because researchers were unable to determine whether treatment was optimal. That was a possible limitation of the study, the researchers noted, as was a failure to follow all participants who had a baseline 24-hour blood pressure study.

Grants from the National Institutes of Health helped to fund the study. The authors had no financial relationships to disclose. ■

## Conscious Sedation Was Safe Despite Apnea Risk

SAN DIEGO — Increased risk for obstructive sleep apnea does not increase the risk for hypoxia in people who undergo standard conscious sedation during endoscopy, based on data from 233 adults presented in a poster at the annual Digestive Disease Week.

Obstructive sleep apnea (OSA) is a growing problem, but few studies have examined whether conscious sedation during an endoscopy puts patients who are at risk for OSA at increased risk for hypoxia.

Dr. Vijay Khiani of Case Western Reserve University, Cleveland, and his colleagues identified 143 endoscopy patients as being at low risk for hypoxia and 90 patients as being at high risk for hypoxia, based on patients' responses to the Berlin Questionnaire, a standard measure of OSA risk.

The mean patient age was 57 years and the mean BMI was 28 kg/m<sup>2</sup>. The low-risk

group included 66 men and 77 women, and the high-risk group included 43 men and 47 women.

Overall, 9 patients (10%) at high risk for OSA and 10 patients (7%) at low risk for OSA became hypoxic during conscious sedation, a non-significant difference. There was no significant difference in the rates of transient hypoxia (defined as a pulse oximetry measure of 92% or less) between the high- and low-risk groups (90% vs. 93%).

Average amounts of sedatives used were 81.4 mg meperidine and 3.6 mg midazolam in the low-risk group and 79.8 mg meperidine and 3.8 mg midazolam in the high-risk group, plus an average of 127.5 mcg and 114.6 mcg fentanyl, respectively, as needed.

Dr. Khiani stated that he had no relevant financial relationships to disclose.

—Heidi Splete

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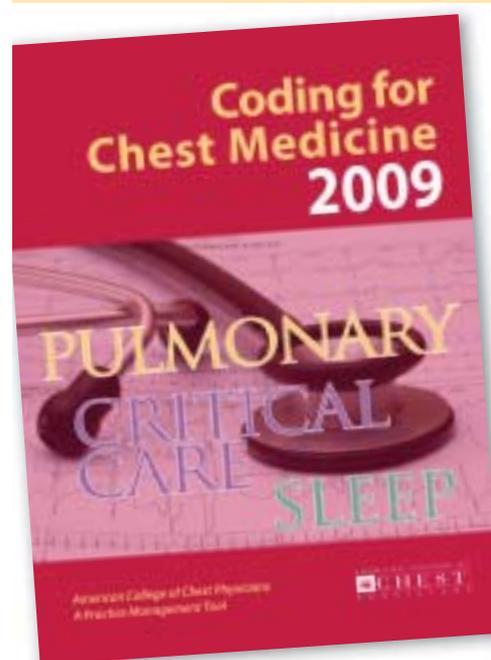
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## NEWS FROM THE COLLEGE



## PRESIDENT'S REPORT

## Looking Back With Thanks, Moving Forward With Hope

It's incredible, but my tenure as the 70th President of the American College of Chest Physicians is coming to an end! It has been a wonderful year! In this report, I will look back over the year, and summarize the highlights for the College and me.

From my perspective, what have been the most prominent College programs, events, and activities this year (since November 2007)?

The *CHEST* journal is an increasingly robust medical journal. It is well organized; the original research articles are of high quality and quite pertinent to our clinical practices; and the special features, such as Topics in Practice Management, Postgraduate Education Corner, Pectoriloquy, and Second Opinion, are wonderful. I give my highest kudos to Editor in Chief Richard Irwin, Executive Editor Stephen J. Welch, and their editorial staff. I also thank the Associate, Section, and International Editors, as well as the Editorial Board, for their high quality contributions to the journal.

The College's advocacy efforts, in cooperation with our sister societies (ATS, ACCN, and SCCM), have been quite successful this year. The Pulmonary Rehabilitation Bill was passed, as part of the Medicare legislative package that eliminated the negative 10.5% cut in physician Medicare reimbursement, after many years of frustrating failure.

We were (and are) able to have substantial impact on the dialogue and decisions in response to the ruling of the Office for Human Research Protection (OHRP) of the US Department of Health and Human Services (HHS) that contradicted the institutional review board (IRB) of Johns Hopkins on the issue of research and quality improvement initiatives and the need for IRBs to scrutinize such processes.

We, in cooperation with our sister societies, have provided comments and are involved in an ongoing manner in the deliberations by the Centers for Medicare and Medicaid Services (CMS) for proposed changes in the Inpatient Prospective Payment Systems for Hospital-Acquired Conditions (HACs).

The College has been increasingly active in the international arena. We actively support our international members' numerous international educational efforts by sending speakers to symposia and endorsing their educational programs. The availability of the online *CHEST* journal to many has also supported that effort. The College is continually trying to

improve and refine our efforts by an active international committee structure (eg, the International Strategy Committee) that has improved the transparency and objectivity of our efforts.

A highlight of the year has been our

continued and increasing cooperation with our sister societies (ATS, ACCN, and SCCM), as well as the Society of Hospital Medicine on issues of common interest, such as the OHRP and HAC issues mentioned. I have been particularly impressed

and pleased with the level of goodwill and cooperation between the College and the ATS. We have been able to work seamlessly on many common issues. I want to give a special thanks to Dr. David Ingbar,

*Continued on following page*

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Continued from previous page

the immediate past president of ATS, who has been fiercely committed to the concept and need for cooperation between our two societies, and to Dr. Jo Rae Wright, current ATS president, who has fostered our joint projects and relationships.

As many of you know, the issues of disparities in health and health care have been a central concern of my presidency. My goal was to have these issues become priority issues for the College, and that has largely happened. At CHEST 2008, the issues will be discussed at several venues and will be presented as part of several clinical symposia.

The issues are very much a part of our national discourse on health insurance during this presidential campaign year, and over the last few years, I have noted an increasing number of articles on disparities in our pulmonary, critical care, and sleep journals (including CHEST). Issues related to care of the underserved must be central issues if we are to substantially improve the quality of US health care.

It has been a great year! Being actively involved in so many essential issues of the College has been a tremendous learning experience. Working with the highly qualified enthusiastic, greatly motivated, and highly professional leadership and staff of the College has been wonderful.

I look forward, with great anticipation, to Dr. James Mathers' upcoming year as ACCP President and wish him the very best. I also want to wish Dr. Kay Guntupalli a wonderful presidential year, as she will succeed Dr. Mathers as President in 2009-2010. What a solid and successful future we have secured for the College with these two great leaders.

It has been an invigorating and humbling experience to be the ACCP President and a distinct privilege for my wife, Zorita (Chair of the Ambassadors Group), and me, to serve the College! We remain committed to the College and all of its programs and activities.

Thank you! ■

Dr. Alvin V. Thomas, Jr., FCCP  
 ACCP President 2007-2008

## This Month in CHEST—Editor's Picks

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

► **Differences in the Response to Methacholine Between the Tidal Breathing and Dosimeter Methods: Influence of the Dose of Bronchoconstrictor Agent Delivered to the Mouth.** By Dr. L. Prieto, et al.

► **Effects of CPAP on Cardiovascular Risk Profile in Patients With Severe Obstructive Sleep Apnea and Metabolic Syndrome.** By Dr. Z. Dorkova, et al.

► **TOPICS IN PRACTICE MANAGEMENT: Practical Guidance for Evidence-Based ICU Family Conferences.** By Dr. J. R. Curtis, FCCP; and Dr. D. B. White.

► **EDITORIAL: Sleeping at Home.** By Dr. I. M. Rosen, FCCP; and Dr. S. Manaker, FCCP.

► **SPECIAL FEATURE: Statins and Interstitial Lung Disease: A Systematic Review of the Literature**



and of FDA Adverse Event Reports. By Dr. A. B. Fernández, et al.

► **CLINICAL COMMENTARY: Alpha-1 Antitrypsin Augmentation Therapy for PI\*<sup>MZ</sup> Heterozygotes: A Cautionary Note.** By Dr. R. A. Sandhaus, et al.

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### USA Programs

**October 25 - 30, 2008**  
 CHEST 2008  
 Philadelphia, PA

**January 22 - 25, 2009**  
 Sleep Medicine 2009  
 Scottsdale, AZ

**February 27 - 28, 2009**  
 Eliminating Borders: STS/ACCP  
 Multidisciplinary Evaluation  
 of Pulmonary/Thoracic Issues  
 Lake Tahoe, CA

**April 3 - 5, 2009**  
 Celebration of Pediatric  
 Pulmonology 2009  
 Scottsdale, AZ

**April 24 - 26, 2009**  
 Fundamentals of Ultrasound  
 Ft. Lauderdale, FL

**August 21 - 24, 2009**  
 Sleep Medicine Board Review 2009  
 Phoenix, AZ

**August 21 - 25, 2009**  
 Critical Care Board Review 2009  
 Phoenix, AZ

**August 25, 2009**  
 Lung Pathology 2009  
 Phoenix, AZ

**August 25, 2009**  
 Mechanical Ventilation 2009  
 Phoenix, AZ

**August 25, 2009**  
 ABIM Critical Care SEP Module 2009  
 Phoenix, AZ

**August 25, 2009**  
 ABIM Pulmonary Disease SEP Module 2009  
 Phoenix, AZ

**August 26 - 30, 2009**  
 Pulmonary Board Review 2009  
 Phoenix, AZ

**October 31 - November 5, 2009**  
 CHEST 2009  
 San Diego, CA

### ACCP Simulation Center for Advanced Clinical Education

Northbrook, Illinois

**November 17 - 20, 2008**  
 Emergency Care Simulator (ECS):  
 Basic and Advanced Course  
 Northbrook, IL

**February 2 - 5, 2009**  
 iStan Basic and Advanced Course  
 Northbrook, IL

**February 13 - 15, 2009**  
 Critical Care Fundamentals  
 Northbrook, IL

**February 20 - 22, 2009**  
 Bronchoscopy Skills  
 Northbrook, IL

**March 6 - 8, 2009**  
 Difficult Airway Management  
 Northbrook, IL

**May 4 - 7, 2009**  
 Human Patient Simulation (HPS):  
 Basic and Advanced Course  
 Northbrook, IL

**November 9 - 12, 2009**  
 Emergency Care Simulator (ECS):  
 Basic and Advanced Course  
 Northbrook, IL

■ ACCP-Sponsored Courses  
 ■ ACCP-Endorsed Courses

### Endorsed International Program

**October 30 - November 2, 2008**  
 Second National Congress of the  
 Bulgarian Respiratory Society  
 Plovdiv, Bulgaria

**November 7, 2008**  
 Symposium on Community-  
 Acquired Pneumonia  
 Lleida, Spain

**November 19 - 22, 2008**  
 13th Congress of the Asian Pacific  
 Society of Respiratory  
 Bangkok, Thailand

**November 21 - 25, 2008**  
 Brazilian Pneumology Congress, ALAT, Brazil-  
 Portugal Congress, Brazilian Bronchology Meeting  
 Brasilia, Brazil

**December 5 - 7, 2008**  
 3rd Asia Pacific Lung Cancer Conference  
 Hyderabad, India

**December 6, 2008**  
 Second Postgraduate Course from the American  
 College of Chest Physicians: Hot Topics and  
 Controversies  
 Oporto, Portugal

**March 7 - 9, 2009**  
 Update on Asthma and COPD  
 Lucknow, India

**January 22 - 24, 2009**  
 ACCP Italian Chapter Biannual Meeting  
 Paestrum, Italy

**March 22 - 23, 2009**  
 IX ACCP Course/ XXIII Central American and  
 the Caribbean Meeting of Pulmonology  
 and Thoracic Surgery  
 San José, Costa Rica

**March 24 - 27, 2009**  
 29th International Symposium on  
 Intensive Care and Emergency Medicine  
 Brussels, Belgium

**April 13 - 17, 2009**  
 XVIII Congress of the Mexican Society  
 of Pulmonology and Thoracic Surgery  
 Veracruz, Mexico

**May 9 - 10, 2009**  
 University Hospital of Lung Diseases  
 Tirania, Albania

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# 2008 - 2009 Education Calendar

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# Pulmonary Perspectives

## COPD and Asthma: Overlapping Histologic and Inflammatory Features—Part 2

*There is a growing body of evidence suggesting that asthma and COPD are not separate entities.*

**B**oth COPD and asthma are chronic inflammatory conditions of the lung associated with alterations of structural components. Differences in these alterations have long been recognized in tissue specimens taken from patients with asthma and COPD selected from polar ends of the clinical spectrum of reversibility and in a stable phase of the disease.

However, there is a growing body of evidence suggesting that asthma and COPD are not separate entities. COPD and asthma may represent disease states along a continuum, with varying degrees of each disease often present in the same patient (see table).

In a subset of patients diagnosed with COPD, eosinophilic inflammation in the airways has been documented. Manage-

ment strategies that aim to minimize eosinophilic airway inflammation are associated with a reduction in severe exacerbations of COPD (Siva et al. *Eur Respir J* 2007; 29:906).

Similarly, a subset of patients clinically diagnosed with COPD that is irreversible in response to an inhaled  $\beta$ -agonist show a partial reversibility of airflow obstruction when treated with 2 weeks of oral corticosteroids.

Research suggests that the responders to corticosteroid therapy may be patients with features of asthma that include reticular basement membrane thickening and eosinophilic inflammation. Such findings support the notion of a significant overlap between these two chronic inflammatory disorders.

In severe asthma, there is epithelial fragility and thickening of the reticular basement membrane, increased airway smooth muscle mass, hypertrophy of mucus-secreting glands, increased vascularity, greater numbers of fibroblasts, and increased deposition of collagen. Biopsy specimens from patients with asthma have demonstrated changes of a similar nature to COPD, but at different degrees and at different anatomic sites.

As more evidence is collected, the

histologic and immunohistologic distinctions between these two conditions become less clear (Jeffery. *Proc Am Thorac Soc* 2004; 1:176).

A neutrophilic pattern of airway inflammation emerges in both asthma and COPD when exacerbations result in hospitalization (Qiu et al. *Thorax* 2007; 62:475). Neutrophil recruitment results from chemoattraction by chemokines, including interleukin-8 (or CXCL8). Furthermore, in mild COPD, exacerbations of bronchitis are associated with

eosinophilia seen in bronchial tissue, and sputum and bronchoalveolar lavage fluid, as well as up-regulation of the eosinophil chemoattractant, RANTES. These two features normally are associated with asthma.

In fatal asthma, increased numbers of

CD8<sup>+</sup> cells have been reported. This mirrors the inflammatory pattern found in mild to moderate COPD and contrasts with the CD4<sup>+</sup> predominance found in mild asthma.

Homogenous thickening and hyaline appearance of the reticular basement membrane are pathognomonic of asthma. Another example of asthma and COPD overlap may be seen in an intermediate thickening of this membrane in mild asthma and COPD, with both conditions demonstrating similar remodeling features (Bourdin et al. *J Allergy Clin Immunol* 2007; 119:1367). A study of eosinophilic bronchitis (Brightling et al. *Thorax* 2003; 58:528) also revealed a thickened reticular basement membrane and further challenges the concept of histopathologic distinctions between asthma and COPD.

### Possible Mechanisms of Evolution From Asthma to COPD

Airway remodeling, or changes in airway structure, occurs in response to chronic injury and inflammation in both asthma and COPD. The presence of airway remodeling may be particularly associated with more severe airflow obstruction, longer duration of disease, and hyperresponsiveness.

COPD is characterized by a slowly progressive, irreversible airflow obstruction; loss of lung elasticity resulting from parenchymal destruction; and peripheral airway inflammation. Small

### Overlapping Histopathologic Features Of COPD and Asthma

Feature	Asthma	COPD
Eosinophilic airway mild inflammation	Yes	Yes—during exacerbations of COPD and in severe COPD
Response to corticosteroid therapy	Yes	Yes—emergence of partial reversibility in subset of patients
Neutrophilic airway inflammation	Yes—during exacerbations	Yes—during exacerbations
Increased CD8 cells	Yes—fatal asthma	Yes
Reticular basement membrane thickening	Yes—pathognomonic	Yes—intermediate thickening

airways dysfunction may play a major role in the progression of asthma to COPD.

Inflammation and fibrosis in the small airways are present in smokers, with and without COPD. The early pulmonary structural changes seen with cigarette smoking result in small airway remodeling by the induction of growth factors in the airway wall (Churg et al. *Am J Respir Crit Care Med* 2006; 174:1327). Remodeling and repair thicken the airway walls, reduce lumen calibre, and restrict the normal increase in caliber produced by lung inflation. Similar structural changes are thought to lead to fixed airway obstruction seen in severe asthma (Bai and Knight. *Clin Sci [Lond]* 2005; 108:463).

Theoretically, this peripheral airway inflammation can lead to airways-parenchyma uncoupling, reducing the elastic load pulling the airways open and resulting in widespread small airway obstruction. Therefore, small airways dysfunction could play a major role in the progression of asthma to COPD, just as smoking-induced lung disease originates in the lung periphery.

Just as Orié and colleagues (*Bronchitis. Assen, Netherlands:*

*Royal van Gorcum*, 1961; 43) had predicted almost 50 years ago, the differentiation between asthma and COPD is modulated by environmental factors (exposure to allergens, respiratory infections, and smoking) and other host factors (airway hyperreactivity, atopy, and genetic predisposition). Future

preventive therapy should target the distal lung, as well as the proximal lung, for effective treatment of asthma.

Only further longitudinal prospective studies will determine whether the availability of effective treatment for childhood asthma targeting the small airways will help prevent the rising rates of COPD in the adult community. ■

Read part 1 of this *Pulmonary Perspectives* article in the September issue of *CHEST Physician* online at [www.chestnet.org/about/publications/chestPhysician.php](http://www.chestnet.org/about/publications/chestPhysician.php).

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### Editor's Insight

**D**r. Eid and colleagues point to new directions in long-term therapeutic trials of patients with asthma. They ask whether attention should be paid to more effective control of airway inflammation during childhood and adolescence in hopes of ensuring maximal lung growth and development during these critical years. Ensuring that lungs grow normally may be an important influence on minimizing the risk for developing irreversible obstructive airway disease in later adulthood.

Dr. Gene L. Colice, FCCP  
Editor, *Pulmonary Perspectives*

**CRITICAL CARE COMMENTARY**

# Improving Lung-Protective Ventilation for ARDS

The syndrome of acute lung injury (ALI) and the more severe subset, acute respiratory distress syndrome (ARDS), affect an estimated 200,000 Americans each year and many more worldwide. Despite evidence that clinicians are making progress in diagnosis and treatment that has led to reductions in mortality, management strategies continue to evolve and, in many cases, provoke controversy.

A cornerstone of current management is to provide mechanical ventilation support, which delivers satisfactory gas exchange while avoiding exacerbation of lung injury. Considerable evidence from *in vitro* research, animal models, and human studies provides a solid rationale for preventing alveolar overdistention, as well as repetitive recruitment-collapse of alveoli. These phenomena, sometimes called “volutrauma” and “atelectrauma,” are intimately tied to the elaboration of proinflammatory cytokines, as well as to recruitment and activation of inflammatory

cells that produce “biotrauma.” This biotrauma is postulated to contribute to multiple organ failure and perpetuate lung injury.

Two of five randomized controlled trials (RCTs) conducted in the 1990s (Amato et al. *Am J Respir Crit Care Med* 1995; 152:1835; Brochard et al. *Am J Respir Crit Care Med* 1998; 158:1831; Brower et al. *Crit Care Med* 1999; 27:1492; Stewart et al. *N Engl J Med* 1998; 338:355; The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000; 342:1301) demonstrated that ventilation with small tidal volumes was associated with lower mortality and shorter duration of ventilation compared with conventional tidal volume ventilation. The first four RCTs were smaller studies ( $\leq 120$  subjects) and arrived at conflicting conclusions.

However, the multicenter RCT (The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000; 342:1301), conducted by National Institutes of Health-funded ARDS Network

investigators, demonstrated the following in 863 subjects with ALI: (1) a significant reduction in mortality and increase in ventilator-free days, and (2) organ failure-free days associated with tidal volumes of 6 mL/kg of predicted body weight (PBW) compared with 12 mL/kg PBW tidal volumes. A metaanalysis of these clinical trials (Petrucci et al. *Cochrane Database Syst Rev* 2004; CD003844) confirms the mortality benefit of ventilation with low tidal volumes, and this strategy has been widely endorsed as beneficial evidence-based practice.

The ventilator parameters used by the ARDS Network investigators included use of the volume-targeted assist control mode, 6 mL/kg PBW tidal volumes, plateau airway pressure (Pplat) levels  $< 30$  cm H<sub>2</sub>O, and the adjustment of respiratory rate to achieve acceptable

acid-base status. A relatively conservative positive end-expiratory pressure (PEEP) approach was used, resulting in PEEP levels averaging 8 to 9 cm H<sub>2</sub>O. Interestingly, oxygenation (PaO<sub>2</sub>/FiO<sub>2</sub>) levels were similar in the 6 mL/kg group and the 12 mL/kg group. This set of parameters was used in the study that demonstrated mortality benefit, so widespread endorsement of these parameters has followed.

Certain aspects of the ARDS Network approach to lung-protective ventilation have been challenged. Specifically, within the context of low tidal volume ventilation (LTVV), what is the role of pressure-targeted ventilation, more liberal Pplat limits, or recruitment maneuvers?

The question of how much PEEP to use for patients with ARDS had been widely debated before LTVV was tested and continues to provoke controversy in the era of lung-protective ventilation. In the other LTVV RCT from the 1990s that yielded positive results, Amato and coworkers (Amato et al. *Am J Respir Crit Care Med* 1995; 152:1835) used pressure-targeted ventilation, allowed Pplat levels as high as 40 cm H<sub>2</sub>O, included recruitment maneuvers when needed, and applied PEEP levels 2 to 3 cm greater than the lower inflection point on a static pressure-volume curve, resulting in an average PEEP value in the 13 to 16 cm H<sub>2</sub>O range.

In other small RCTs that targeted low tidal volume and higher PEEP values (Ranieri et al. *JAMA* 1999; 282:54; Villar et al. *Crit Care Med* 2006; 34:1311), positive results have been demonstrated in direct comparisons with conventional ventilation, including reductions in alveolar and systemic inflammation, better

oxygenation, shorter duration of mechanical ventilation support, and lower mortality.

In subsequent RCTs (Brower et al. *N Engl J Med* 2004; 351:327), the ARDS Network investigators compared high-PEEP and low-PEEP strategies in 549 subjects. PEEP and FiO<sub>2</sub> levels were adjusted according to a table for each arm of the study, resulting in average PEEP values of 13.2 cm H<sub>2</sub>O and 8.3 cm H<sub>2</sub>O for the two groups, respectively. While oxygenation was significantly better with higher PEEP levels, there were no differences in frequency of barotraumas, duration of mechanical ventilation support, or mortality between groups. A substudy of this RCT (Brower et al. *Crit Care Med* 2003; 31:2592) examined the effects

of recruitment maneuvers (40 cm H<sub>2</sub>O pressure for 30 s), which had no sustained impact on gas exchange.

Earlier this year, the results of two large multicenter RCTs that examined various features of lung protective ventilation for ALI were published. These studies examined PEEP strategies and other variables in the delivery of LTVV that should influence patient care. Meade and coinvestigators (*JAMA* 2008; 299:637) studied 983 patients with ALI and compared low tidal volume ventilation, using traditional ARDS Network parameters, with an open-lung strategy modeled on parameters from Amato's approach, as previously described. The two approaches yielded very similar outcomes, including outcomes for all-cause hospital mortality, duration of ventilation, and barotrauma. The open-lung approach resulted in higher PaO<sub>2</sub>/FiO<sub>2</sub>, lower rates of refractory hypoxemia, and less use of rescue therapies, such as inhaled nitric oxide, prone positioning, high-frequency ventilation, or extracorporeal membrane oxygenation.

Mercat and colleagues (*JAMA* 2008; 299:646) compared an “increased recruitment strategy” that resulted in higher PEEP values (averaging 13.4 cm H<sub>2</sub>O on day three) with a “minimal distention strategy,” with PEEP values averaging 6.7 cm H<sub>2</sub>O on day three. Delivery of tidal volumes of 6 mL/kg PBW by volume-targeted assist control was used in both groups in this RCT of 767 patients with ALI. Using a novel approach, PEEP levels were increased progressively, as long as the Pplat level was  $< 28$  to 30 cm H<sub>2</sub>O, and, subsequently, PEEP was reduced using a defined strategy. The increased recruitment strategy was associated with better oxygenation, lower utilization of rescue therapies, and more ventilator-free and organ

*Continued on following page*

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## NEWS FROM THE COLLEGE



Continued from previous page

failure-free days, with no difference in barotraumas or mortality. While this approach may be well-suited to the stiff lungs of patients with severe ARDS, when applied to patients with milder forms of lung injury, alveolar overdistention may result. In fact, the reduction in duration of ventilation support and trend for lower mortality seen in patients with

ARDS was lost in patients with  $\text{PaO}_2/\text{FiO}_2$  levels of 200 to 300 mm Hg.

One can conclude from the cumulative study results that the primary goal is delivery of lung-protective ventilation with tidal volumes of 6 mL/kg PBW using volume-targeted or pressure-targeted ventilation. Use of a more aggressive early PEEP strategy combined with a PEEP de-escalation plan for patients with ARDS, but perhaps not for patients with ALI without ARDS,

is supported by recent research.

The use of low tidal volume ventilation for patients with ARDS is widely regarded as one of the few high-level evidence-based strategies in critical care medicine, yet it is often not used by clinicians. Several studies (Weinert et al. *Am J Respir Crit Care Med* 2003; 167:1304; Young et al. *Crit Care Med* 2004; 32:1260) showed that low tidal volumes were rarely used, even in ARDS Network centers. Surveys by Rubenfeld and

colleagues (*Crit Care Med* 2004; 32:1289) shed some light on underlying factors for physicians not initiating low tidal volume ventilation, such as lack of recognition of ALI, unwillingness to relinquish control of the ventilator, concern about contraindications, and concern about not continuing ventilation support (ie, concerns about gas exchange and patient comfort). Interestingly, the need for sedative and paralytic drugs was not different between low and conventional tidal volume study groups (Cheng et al. *Crit Care Med* 2005; 33:63).

Recent reports (Checkley et al. *Am J Respir Crit Care Med* 2008; 177:1215; Umoh et al. *Crit Care Med* 2008; 36:1463) offer encouragement that low tidal volume ventilation is being used more frequently. Of particular interest is the finding that the strongest independent risk factor for use of low tidal volume ventilation is the use of a written protocol (Umoh et al. *Crit Care Med* 2008; 36:1463). Such protocols should streamline calculation of tidal volume and predicted body weight, calculated based upon height from the following equations:

► Men:  $\text{PBW} = 50 \text{ kg for } 60 \text{ inches in height} + 2.3 \text{ kg/inch above } 60 \text{ inches}$

► Women:  $\text{PBW} = 45.5 \text{ kg for } 60 \text{ inches in height} + 2.3 \text{ kg/inch above } 60 \text{ inches}$

Calculations for 6 mL/kg PBW tidal volumes reveal that most men (those shorter than 6 feet 2 inches) require tidal volumes <500 mL, and most women (shorter than 5 feet 8 inches) require tidal volumes <400 mL.

In summary, the results of recent RCTs build upon work that supports the use of low tidal volume ventilation for patients with ALI, as well as higher PEEP earlier in the course of ARDS. Broad application of lung-protective ventilation for all patients who might benefit will be improved through consistent use of explicit written protocols in the ICU. ■

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## October PCGU

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### ► Weaning From Mechanical Ventilation

By Dr. Timothy D. Girard; and Dr. E. Wesley Ely, Jr., FCCP

### ► Drug-Induced Acute Kidney Injury in the ICU

By Dr. Ghousia Wajida; and Dr. Richard Fatica

**Table 1:** Adverse Reactions with  $\geq 3\%$  Incidence Reported in Patients  $\geq 12$  Years of Age with ALVESCO in US Placebo-Controlled Clinical Trials in Patients Previously on Bronchodilators and/or Inhaled Corticosteroids

Adverse Reaction	Placebo (N=507) %	ALVESCO		
		80 mcg BID (N=325) %	160 mcg BID (N=127) %	320 mcg BID (N=172) %
Headache	7.3	4.9	11.0	8.7
Nasopharyngitis	7.5	10.5	8.7	7.0
Sinusitis	3.0	3.1	5.5	5.2
Pharyngolaryngeal pain	4.3	4.3	2.4	4.7
Upper respiratory Inf.	6.5	7.1	8.7	4.1
Arthralgia	1.0	0.9	2.4	3.5
Nasal congestion	1.6	1.8	5.5	2.9
Pain in extremity	1.0	0.3	3.1	2.3
Back pain	2.0	0.6	3.1	1.2

The following adverse reactions occurred in these clinical trials using ALVESCO with an incidence of less than 1% and occurred at a greater incidence with ALVESCO than with placebo.

#### Infections and Infestations:

Oral candidiasis

#### Respiratory Disorders:

Cough

#### Gastrointestinal Disorders:

Dry mouth, nausea

#### General disorders and administrative site conditions:

Chest discomfort

#### Respiratory, Thoracic, and Mediastinal Disorders:

Dysphonia, dry throat

The fifth study was a 12-week clinical trial in asthma patients 12 years of age and older who previously required oral corticosteroids (average daily dose of oral prednisone of 12 mg/day), in which the effects of ALVESCO 320 mcg twice daily (n = 47) and 640 mcg twice daily (n = 49) were compared with placebo (n=45) for the frequency of reported adverse reactions. The following adverse reactions occurred at an incidence of  $\geq 3\%$  in the ALVESCO-treated patients and were more frequent compared to placebo: sinusitis, hoarseness, oral candidiasis, influenza, pneumonia, nasopharyngitis, arthralgia, back pain, musculoskeletal chest pain, headache, urticaria, dizziness, gastroenteritis, face edema, fatigue, and conjunctivitis.

#### Pediatric Patients 4 to 11 Years of Age

The safety of ALVESCO in pediatric patients 4 to 11 years of age was evaluated in two studies in which ALVESCO 40 mcg, 80 mcg, and 160 mcg was administered once daily for 12 weeks.

#### Pediatric Patients under 4 Years of Age

Studies have not been conducted in patients under 4 years of age.

#### Long-Term Clinical Trials Experience

A total of 197 patients 12 years of age and older (82 males and 115 females) from one of the 12-week treatment placebo-controlled studies were re-randomized to ciclesonide 320 mcg twice daily and followed for one year. The safety profile from the one-year follow up was similar to that seen in the 12- and 16-week treatment studies. Long term safety information for pediatric patients 4 to 11 years of age is obtained from three open label one year safety studies.

#### Post-marketing Experience

In addition to adverse reactions identified from clinical trials, the following adverse reactions have been identified during worldwide post-marketing use of ciclesonide oral inhalation. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: Immediate or delayed hypersensitivity reactions such as angioedema with swelling of the lips, tongue and pharynx.

#### DRUG INTERACTIONS

In clinical studies, concurrent administration of ciclesonide and other drugs commonly used in the treatment of asthma (albuterol, formoterol) had no effect on pharmacokinetics of des-ciclesonide.

*In vitro* studies and clinical pharmacology studies suggested that des-ciclesonide has no potential for metabolic drug interactions or protein binding-based drug interactions.

In a drug interaction study, co-administration of orally inhaled ciclesonide and oral ketoconazole, a potent inhibitor of cytochrome P450 3A4, increased the exposure (AUC) of des-ciclesonide by approximately 3.6-fold at steady state, while levels of ciclesonide remained unchanged.

#### USE IN SPECIFIC POPULATIONS

##### Pregnancy

##### Teratogenic Effects: Pregnancy Category C

Oral administration of ciclesonide in rats up to 900 mcg/kg/day (approximately 10 times the maximum human daily inhalation dose based on mcg/m<sup>2</sup>/day) produced no teratogenicity or other fetal effects. However, subcutaneous administration of ciclesonide in rabbits at 5 mcg/kg/day (less than the maximum human daily inhalation dose based on mcg/m<sup>2</sup>/day) or greater produced fetal toxicity. This included fetal loss, reduced fetal weight, cleft palate, skeletal abnormalities including incomplete ossifications, and skin effects. No toxicity was observed at 1 mcg/kg (less than the maximum human daily inhalation dose based on mcg/m<sup>2</sup>).

There are no adequate and well-controlled studies in pregnant women. ALVESCO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Experience with oral corticosteroids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

##### Non-teratogenic Effects:

Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully monitored.

##### Nursing Mothers

It is not known if ciclesonide is secreted in human milk. However, other corticosteroids are excreted in human milk. In a study with lactating rats, minimal, but detectable levels of ciclesonide were recovered in milk. Caution should be used when ALVESCO is administered to nursing women.

##### Pediatric Use

The safety and effectiveness of ALVESCO in children under 12 years of age have not been established.

Two randomized double-blind placebo-controlled studies were conducted to evaluate the efficacy of ALVESCO 40, 80, or 160 mcg administered once daily for 12 weeks in patients 4 to 11 years of age with asthma. These studies included 1018 patients previously using either controller therapy (predominately inhaled corticosteroids) or reliever therapy (bronchodilator therapy alone). The patients had a mean baseline percent predicated FEV<sub>1</sub> of 68%. The primary efficacy endpoint was morning pre-dose FEV<sub>1</sub>. Other measures of efficacy included AM PEF, asthma symptoms, and rescue albuterol use. The studies showed inconsistent results and do not establish the efficacy of ALVESCO in patients 4 to 11 years of age.

The safety of ALVESCO was evaluated in 957 children between the ages of 4 and 11 who were treated with ALVESCO in the two controlled clinical studies, 2 open label one-year safety extensions of the controlled clinical studies, and one open label safety study. In the controlled studies, the distribution of adverse events in the ALVESCO and placebo groups was similar. The type of adverse events reported were similar to events reported in this patient population with other inhaled corticosteroids. The open label safety studies compared the safety of ALVESCO in doses up to 160 mcg once daily with an orally inhaled corticosteroid comparator. The types of adverse events seen were similar to those seen in the 12-week controlled studies.

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

A 52-week, multi-center, double-blind, randomized, placebo-controlled parallel-group study was conducted to assess the effect of orally inhaled ciclesonide on growth rate in 609 pediatric patients with mild persistent asthma, aged 5 to 8.5 years. Treatment groups included orally inhaled ciclesonide 40 mcg or 160 mcg or placebo given once daily. Growth was measured by stadiometer height during the baseline, treatment and follow-up periods. The primary comparison was the difference in growth rates between ciclesonide 40 and 160 mcg and placebo groups. Conclusions cannot be drawn from this study because compliance could not be assured. There was no difference in efficacy measures between the placebo and the ALVESCO groups. Ciclesonide blood levels were also not measured during the one-year treatment period.

The potential growth effects of prolonged treatment with orally inhaled corticosteroids should be weighed against clinical benefits obtained and the availability of safe and effective noncorticosteroid treatment alternatives. To minimize the systemic effects of orally inhaled corticosteroids, including ALVESCO, each patient should be titrated to his/her lowest effective dose.

#### Geriatric Use

Clinical studies of ALVESCO did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

#### OVERDOSAGE

Chronic overdosage may result in signs/symptoms of hypercorticism. ALVESCO was well tolerated following inhalation by healthy subjects of single doses of 2880 mcg. A single oral dose of up to 10 mg of ciclesonide in healthy subjects was well tolerated and serum cortisol levels were virtually unchanged in comparison with placebo treatment. Adverse reactions were of mild or moderate severity.

The median lethal doses in mice and rats after single oral and intraperitoneal administration were >2000 mg/kg and >200 mg/kg, respectively. These doses are >12000 and >2500 times the maximum recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis.

#### Carcinogenesis, Mutagenesis, Impairment of Fertility

Ciclesonide demonstrated no carcinogenic potential in a study of oral doses up to 900 mcg/kg/day (approximately 6 times the maximum human daily inhalation dose based on mcg/m<sup>2</sup>/day) in mice for 104 weeks and in a study of inhalation doses up to 193 mcg/kg/day (approximately 2 times the maximum human daily inhalation dose based on mcg/m<sup>2</sup>/day) in rats for 104 weeks.

Ciclesonide was not mutagenic in an Ames test or in a forward mutation assay and was not clastogenic in a human lymphocyte assay or in an *in vitro* micronucleus test. However, ciclesonide was clastogenic in the *in vivo* mouse micronucleus test. The concurrent reference corticosteroid (dexamethasone) in this study showed similar findings.

No evidence of impairment of fertility was observed in a reproductive study conducted in male and female rats both dosed orally up to 900 mcg/kg/day (approximately 10 times the maximum human daily inhalation dose based on mcg/m<sup>2</sup>/day).



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**NETWORKS**

# Palliative Care, Women's Health, Practice Administration

**Palliative and End-of-Life Care**

A significant challenge for all of modern medicine is the task of translating the growing evidence base from efficacy trials into clinical practice. The National Institutes of Health has been transforming the research enterprise with the hope of more rapid implementation and uptake of new discoveries. Studies have demonstrated the importance of enhancing family communication as a part of best practices in the ICU, and guidelines and statements cite the data showing that improved family communication benefits overall care, ICU utilization, and family outcomes.

However, changing routine practice requires locally adaptive strategies and novel tools to aid practitioners and delivery systems to incorporate expanding knowledge. To advance provider-family communication, V.A.L.U.E. has emerged as a brilliant new approach. The V.A.L.U.E. acronym combines five evidence-based

practices in family communication, resulting in an easy clinical reminder for practitioners to take advantage of opportunities to listen and respond within a paradigm of shared decision-making and family-inclusive interdisciplinary care. V.A.L.U.E. stands for the following: Value and appreciate what family members say; Acknowledge family members' emotions; Listen actively and empathetically; Understand the patient as a person; and Elicit questions from family.

Critical care requires technical and specialized skills, including palliative care, which has always emphasized effective patient- and family-centered communication. It is essential that such care be offered concomitantly with life-preserving therapy for all ICU patients. For patients in the ICU who experience the end of life, family members become both partners and recipients of care. As one important way to start realizing improved translation from scientific discovery into better

societal health, V.A.L.U.E. is ready for ICU practice enhancement and quality innovation efforts.

*Dr. Richard A. Mularski, FCCP  
Palliative and End-of-Life Care  
Steering Committee Member*

**Women's Health**

Tobacco companies have a long-standing relationship with Hollywood, including compensating actors to smoke their brands of cigarettes and paying producers to place tobacco products in their films. The 1998 Master Settlement Agreement attempted to address this issue by prohibiting tobacco companies from paying to place their products in movies. However, this practice continues. Hollywood promotes tobacco use as glamorous, rebellious, and a desirable social norm. The negative depictions of tobacco use are rarely shown.

Why is this important? Research

shows that smoking in movies contributes to smoking initiation in youth. Kids exposed to smoking in films have a higher likelihood of using tobacco and are twice as likely to smoke when their favorite stars smoke on screen. Advocates have been calling on Hollywood to stop allowing this method of recruitment.

Hollywood is starting to respond. Last year, the Motion Picture Association of America (MPAA) announced that it would consider smoking as a factor in the rating of films. In July 2008, six Hollywood studios agreed to place anti-smoking public service announcements on all DVDs rated G, PG, and PG-13 that included tobacco use. The State of California will provide the antismoking spots. As welcomed as these steps are, they are not meeting Smoke Free Movies' four policy recommendations endorsed by health advocates nationwide.

Smoke Free Movies, a project of

*Continued on following page*

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## NEWS FROM THE COLLEGE

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*Continued from previous page*

Stanton Glantz, PhD, has outlined the following four steps Hollywood can take to substantially reduce the impact of adolescent exposure to smoking on screen: (1) Rate new movies that include tobacco use as "R"; (2) Certify that no payoffs are received; (3) Require strong antismoking ads to run before any film that contains tobacco use; and (4) Stop showing tobacco brands or imagery in the background of movie scenes. To learn more about this campaign, visit [www.smokefreemovies.ucsf.edu](http://www.smokefreemovies.ucsf.edu).

The AMA Alliance launched the "Screen Out!" campaign to garner support for the Smoke Free Movies project. The campaign uses members nationwide to pressure media companies and the MPAA to remove tobacco use from youth-rated Hollywood films. To join this campaign, visit [www.amaalliance.org](http://www.amaalliance.org).

Virginia Reichert, NP  
 Women's Health  
 Steering Committee Member;  
 Patricia Folan, RN;  
 and Susan Kennedy, LMSW, CASAC

### Practice Administration

One of the many benefits of ACCP membership is participation in one or more of the 25 NetWorks. ACCP NetWorks provide education, information, direct consultation, and leadership opportunities relative to specific clinical areas, practice operations, or community health issues.

There is an incredible value in belonging to a NetWork. I have been a member of the Practice Administration, Private Practice, and Sleep Medicine NetWorks for the past 5 years, and I have gained valuable information and contacts that I have used as a practice administrator for a six-physician pulmonary medicine group.

Do you have concerns about maintaining physician compensation in an environment of declining reimbursement, controlling your practice's operating costs, selecting an electronic medical record system, forming alliances or contracts with hospitals, recruiting new physicians to your

practice, and/or maintaining your current clinical knowledge?

If you answered yes to any of the above, what is your plan to address these issues for your practice(s)? Do you have a practice administrator or manager who has knowledge to address these issues? One of the values of a NetWork is gaining useful and practical information.

The Practice Administration NetWork comprises physicians, practice administrators, and managers who are addressing these issues. The NetWork provides members with various forms of education on issues through publications, sessions at the annual CHEST meetings, and NetWork conference calls.

Surprisingly, not many practice administrators are aware that they can become members of the ACCP. If you are already a member of the ACCP, I strongly encourage you to join and participate in the Practice Administration NetWork. If you are a physician and have a practice administrator or manager, I encourage you to have him or her join the ACCP as an allied health member, as well as join the Practice Administration NetWork. The cost for allied health membership is only \$60 per year. My experience has been professionally rewarding, and I am certain that yours will be, too.

Michael K. McCormick, RRT, MBA  
 Practice Administration  
 Vice-Chair

### Transplant

The Transplant NetWork is committed to enhancing the care of lung transplant candidates and recipients through projects that disseminate information to both the professional and patient communities. Important projects completed in the past include a survey of clinical practices among North American lung transplant centers (*Chest* 2004; 125:1224) and Web-based guides to lung transplantation for patients and community pulmonologists. The Transplant NetWork is now involved in two new projects that address areas of major importance in the field.

The first project is a proposed consensus statement on management of the organ donor in the ICU. This project would be a collaborative effort between the

Transplant, Critical Care, and Palliative and End-of-Life Care NetWorks. The Society of Critical Care Medicine, American Association of Critical-Care Nurses, American Thoracic Society, American Academy of Pediatrics, and the United Network for Organ Sharing are potential collaborating organizations. Through rigorous literature review and expert opinion, the project seeks to define and standardize optimal practices in the management of organ donors. The working group hopes to publish the document in one of the collaborating organization's journals. We view this project as vital to ongoing national efforts to expand the organ donor pool at a time when demand continues to outpace the supply.

The second project involves a rigorous and systematic examination of barriers to optimal palliative care of lung transplant candidates. It is a collaborative project with the Transplant, Interstitial and Diffuse Lung Disease, and the Palliative and End-of-Life Care NetWorks. This project recognizes the potential conflict created in placing patients with advanced lung disease on the aggressive path of transplant listing, while concurrently trying to ensure that end-of-life and palliative care issues are addressed. A survey has been created that, once validated, will be sent to all members of the Transplant NetWork for completion. A scholarly publication is the anticipated outcome of this project.

We encourage ACCP members with an interest in the field of transplantation to join in all of the activities of our NetWork. These activities promote collaboration and scholarship and, ultimately, advance the field of transplantation for the benefit of our patients. Visit the Transplant NetWork Web pages at [www.chestnet.org/networks/transplant/index.php](http://www.chestnet.org/networks/transplant/index.php) for additional information.

Dr. Robert Kotloff, FCCP  
 Transplant  
 Chair

### Affiliate

In order to better serve the junior members of the College, the Affiliate NetWork Steering Committee developed a survey for Affiliate members. A 15-question survey was sent via e-mail to 947 Affiliate members, and 140 members responded. We discovered that 51% of respondents had not attended the annual CHEST meeting. Of those who had attended CHEST, a majority (>60%) attended the case report sessions and the CHEST Challenge. Thirty percent attended the NetWork luncheon. A minority attended sessions on how to do a presentation, how to succeed in academic medicine, and education program development (3.2 to 12.9%). When asked how likely they would be to attend a session on various topics, the greatest number of responses was focused on pulmonary education and board review.

Many of the Affiliate member survey respondents would like a Web-based message board and reading list on clinical subjects, and 44% thought that membership in the ACCP was very valuable. They also would like to have the Affiliate NetWork focus on preparation for board exams and offer opportunities to interact with leaders in the field.

In summary, the survey of Affiliate members has been helpful in better defining our role as a NetWork. We have done extremely well in growing participation in the CHEST Challenge and Affiliate case report sessions. However, our constituents would appreciate clinical-pathologic conference discussion, board review preparatory sessions, and opportunities to interact with leading experts in the future. The Affiliate NetWork will adjust its focus accordingly to satisfy our members' needs.

Dr. Kevin Chan, FCCP  
 Affiliate NetWork Chair

*Continued on page 19*

## Master Fellow Receives Prestigious Award

Dr. Allen I. Goldberg, Master FCCP, a Past President of the ACCP, has been honored by his medical school alma mater. The Clark-Curran Award for outstanding leadership in medical administration was awarded to Dr. Goldberg in June, as he celebrated his 40th year following his graduation from the State University of New York, Downstate Medical Center. This is a very prestigious award and is one of the highest nonteaching



DR. ALLEN I. GOLDBERG

awards offered by SUNY Downstate to its alumni. The Clark-Curran award is named in honor of Dr. Duncan Clark, a 1936 graduate from Downstate who served as Dean and President of SUNY Downstate; and Dr. Alonzo Curran, a former President of the Long Island College Hospital, the forerunner of SUNY Downstate Hospital.

The ACCP and The CHEST Foundation congratulate Dr. Goldberg on this distinguished honor. ■

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## PROFESSIONAL OPPORTUNITIES

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This location is on the Gulf of Mexico and next to the Caloosahatchee River; this city offers ponds, lakes and canals. Some of Florida's finest beaches are at Bonita Beach, Ft. Myers Beach, Captiva and Sanibel Islands. Boating enthusiasts can enjoy a direct channel west to the Gulf of Mexico and east to the Atlantic Ocean and north to mid-state Florida. Within the community, residents enjoy year-round freshwater fishing, golf at five championship courses, biking, tennis, walking and numerous recreational facilities, entertainment opportunities and schools abound!! This established practice is looking to expand due to growth. Excellent compensation plus production bonus, benefits and partnership track. Income potential will exceed 90th percentile of MGMA. Average patient volume daily is outpatient (15-20%) and inpatient (10-15%); practice focus: pulmonary (40%), critical care (30%), sleep (30%). Eric Rubin, Phone: 888-647-5005, ext. 221, Fax: 800-793-8028, [erubin@nhpartners.com](mailto:erubin@nhpartners.com)

### Pulmonary/ Critical Care Physician

Pulmonary/ Critical Care Physician sought for - IL/MO (St. Louis region). This excellent employed position is ideal for someone who seeks Directorship of an ICU. Physicians completing training are also encouraged to apply. Practice consists of 80% Critical Care 20% Pulmonary. ICU is seven beds with census of four - five patients. Must be BE/BC located within 20 minutes of St. Louis. Enjoy small community/suburban or city living. Competitive compensation, production bonus, full benefits and relocation offered. To expedite consideration reply with your CV to: Merie Mann PH: 314-409-8800 [mmann@mannelc.com](mailto:mmann@mannelc.com) or FAX: 636-536-1729. This opportunity does not qualify for J-1 visa waiver.

### Suburban Pittsburgh

Pulmonary and Sleep Medicine Physician needed in suburban Pittsburgh, PA. Excellent salary and fringe benefits. Equal Opportunity Employer. J-1 Visa consideration. Please send CV to Chest #84, P.O. Box 996, Abingdon, MD 21009.

### North Shore, Long Island

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Sutter Auburn Faith Hospital is a medium sized hospital with a 24/7 hospitalist program, open ICU, high resolution CT scan, cardiac cath lab, full nuclear medicine department, bronchoscopy suites and a pulmonary function laboratory.

Auburn is centrally located in the Sierra Nevada foothills between Sacramento and Lake Tahoe. Auburn is close to shopping and restaurants, and offers a variety of outdoor activities.

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The community of Auburn is nestled in the Sierra Nevada Foothills approximately 35 miles northeast of Sacramento. Auburn is known for its family-oriented atmosphere and for its excellent schools. Residents enjoy year-round outdoor recreations such as golfing, hiking, biking, and white water rafting.



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Continued from page 17

### Airways Disorders

During the 20th century, enormous resources were devoted to medical discovery. COPD received comparatively little attention, and yet, during the decades of the 1970s through the 1990s, mortality for COPD rose in this country by 163%.

In response to these alarming statistics, there has been an intense research effort to better understand the pathogenesis of COPD and new approaches to treatment. While the pulmonary community has shown renewed interest in COPD as a "preventable and treatable" disease, there has been a lag in disseminating new advances regarding COPD to the primary care community.

In 2007, I was granted the Second GlaxoSmithKline Distinguished Scholar in Respiratory Health award. The objective of my project is to develop an integrated COPD chronic care model for primary care physicians and other health-care providers, encouraging high-quality, evidence-based and guideline-driven chronic disease management for COPD. The COPD chronic care model is being developed through a partnership with members of the Airways Disorders NetWork, members of the Institute for Healthcare Improvement (IHI), and community-based primary care physicians.

In May, during phase I of the project, a meeting was held to summarize current COPD guideline recommendations and discuss how they can be incorporated into a delivery system that will be user-friendly for providers, patients, and their families. Participants included Dr. Paula Anderson, FCCP, Dr. Jay Peters, FCCP, Dr. Nicola Hanania, MBBS, FCCP, and Dr. Sandra Adams, FCCP,

from the Airways Disorders NetWork Steering Committee; Dr. Lawrence Mohr, Jr., FCCP, of The CHEST Foundation Board of Trustees; John Walsh, CEO of the Alpha-1 Foundation; and Marie Schall, IHI Director, Dr. Sean Townsend, FCCP, IHI faculty, and Susan Went, IHI Fellow. Additional participants were Dr. Sydney Parker and Dr. David Eubanks from the ACCP.

I have been encouraged and assisted

by the Department of Family Medicine of Brown University in creating the COPD chronic care model.

Dr. Joshua Gutman, a family practice physician and member of the department, attended the May meeting and is working with me on the next phase of the project. He is a member of a group in Rhode Island called Quality Partners, sponsored by the Rhode Island Department of Health.

The Rhode Island Department of Health is a network of primary care physicians who have used a chronic care model for diabetes mellitus and, over the next year, will be the first site to test the ACCP COPD Chronic Care Model. ■

Dr. Sidney S. Braman, FCCP  
Second GlaxoSmithKline Distinguished  
Scholar in Respiratory Health

### BRIEF SUMMARY OF PRESCRIBING INFORMATION

## CSL Behring Zemaira® Alpha<sub>1</sub>-Proteinase Inhibitor (Human)

Manufactured by:  
CSL Behring LLC  
Kankakee, IL 60901 USA  
US License No. 1767

#### Ⓡ only

Before prescribing, please consult full prescribing information, a brief summary of which follows:

#### INDICATIONS AND USAGE

Zemaira® is indicated for chronic augmentation and maintenance therapy in individuals with alpha<sub>1</sub>-proteinase inhibitor (A<sub>1</sub>-PI) deficiency and clinical evidence of emphysema.

Zemaira® increases antigenic and functional (ANEC) serum levels and lung epithelial lining fluid levels of A<sub>1</sub>-PI. Clinical data demonstrating the long-term effects of chronic augmentation therapy of individuals with Zemaira® are not available.

Safety and effectiveness in pediatric patients have not been established.

Zemaira® is not indicated as therapy for lung disease patients in whom severe congenital A<sub>1</sub>-PI deficiency has not been established.

#### CONTRAINDICATIONS

Zemaira® is contraindicated in individuals with a known hypersensitivity to any of its components. Zemaira® is also contraindicated in individuals with a history of anaphylaxis or severe systemic response to A<sub>1</sub>-PI products.

Individuals with selective IgA deficiencies who have known antibodies against IgA (anti-IgA antibodies) should not receive Zemaira®, since these patients may experience severe reactions, including anaphylaxis, to IgA that may be present in Zemaira®.

#### WARNINGS

Zemaira® is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. Because Zemaira® is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically the Creutzfeldt-Jakob disease (CJD) agent. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses during manufacture. (See **DESCRIPTION** section for viral reduction measures.) The manufacturing procedure for Zemaira® includes processing steps designed to reduce further the risk of viral transmission. Stringent procedures utilized at plasma collection centers, plasma testing laboratories, and fractionation facilities are designed to reduce the risk of viral transmission. The primary viral reduction steps of the Zemaira® manufacturing process are pasteurization (60°C for 10 hours) and two sequential ultrafiltration steps. Additional purification procedures used in the manufacture of Zemaira® also potentially provide viral reduction. Despite these measures, such products may still potentially contain human pathogenic agents, including those not yet known or identified. Thus, the risk of transmission of infectious agents can not be totally eliminated. Any infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to CSL Behring at 800-504-5434. The physician should discuss the risks and benefits of this product with the patient. Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections (see **Information For Patients**).

During clinical studies, no cases of hepatitis A, B, C, or HIV viral infections were reported with the use of Zemaira®.

#### PRECAUTIONS

**General** - Infusion rates and the patient's clinical state should be monitored closely during infusion. The patient should be observed for signs of infusion-related reactions.

As with any colloid solution, there may be an increase in plasma volume following intravenous administration of Zemaira®. Caution should therefore be used in patients at risk for circulatory overload.

**Information For Patients** - Patients should be informed of the early signs of hypersensitivity reactions

including hives, generalized urticaria, tightness of the chest, dyspnea, wheezing, faintness, hypotension, and anaphylaxis. Patients should be advised to discontinue use of the product and contact their physician and/or seek immediate emergency care, depending on the severity of the reaction, if these symptoms occur.

As with all plasma-derived products, some viruses, such as parvovirus B19, are particularly difficult to remove or inactivate at this time. Parvovirus B19 may most seriously affect pregnant women and immune-compromised individuals. Symptoms of parvovirus B19 include fever, drowsiness, chills, and runny nose followed two weeks later by a rash and joint pain. Patients should be encouraged to consult their physician if such symptoms occur.

**Pregnancy Category C** - Animal reproduction studies have not been conducted with Zemaira®, Alpha<sub>1</sub>-Proteinase Inhibitor (Human). It is also not known whether Zemaira® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Zemaira® should be given to a pregnant woman only if clearly needed.

**Nursing Mothers** - It is not known whether Zemaira® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Zemaira® is administered to a nursing woman.

**Pediatric Use** - Safety and effectiveness in the pediatric population have not been established.

**Geriatric Use** - Clinical studies of Zemaira® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. As for all patients, dosing for geriatric patients should be appropriate to their overall situation.

#### ADVERSE REACTIONS

Intravenous administration of Zemaira®, 60 mg/kg weekly, has been shown to be generally well tolerated. In clinical studies, the following treatment-related adverse reactions were reported: asthenia, injection site pain, dizziness, headache, paresthesia, and pruritus. Each of these related adverse events was observed in 1 of 89 subjects (1%). The adverse reactions were mild.

Should evidence of an acute hypersensitivity reaction be observed, the infusion should be stopped promptly and appropriate countermeasures and supportive therapy should be administered.

Table 3 summarizes the adverse event data obtained with single and multiple doses during clinical trials with Zemaira® and Prolastin®. No clinically significant differences were detected between the two treatment groups.

Table 3: Summary of Adverse Events

	Zemaira®	Prolastin®
No. of subjects treated	89	32
No. of subjects with adverse events regardless of causality (%)	69 (78%)	20 (63%)
No. of subjects with related adverse events (%)	5 (6%)	4 (13%)
No. of subjects with related serious adverse events	0	0
No. of infusions	1296	160
No. of adverse events regardless of causality (rates per infusion)	298 (0.230)	83 (0.519)
No. of related adverse events (rates per infusion)	6 (0.005)	5 (0.031)

The frequencies of adverse events per infusion that were ≥0.4% in Zemaira®-treated subjects, regardless of causality, were: headache (33 events per 1296 infusions, 2.5%), upper respiratory infection (1.6%), sinusitis (1.5%), injection site hemorrhage (0.9%), sore throat (0.9%), bronchitis (0.8%), asthenia (0.6%), fever (0.6%), pain (0.5%), rhinitis (0.5%), bronchospasm (0.5%), chest pain (0.5%), increased cough (0.4%), rash (0.4%), and infection (0.4%).

The following adverse events, regardless of causality, occurred at a rate of 0.2% to <0.4% per infusion: abdominal pain, diarrhea, dizziness, ecchymosis, myalgia, pruritus, vasodilation, accidental injury, back pain, dyspepsia, dyspnea, hemorrhage, injection site reaction, lung disorder, migraine, nausea, and paresthesia. Diffuse interstitial lung disease was noted on a routine chest x-ray of one subject at Week 24. Causality could not be determined.

In a retrospective analysis, during the 10-week blinded portion of the 24-week clinical study, 6 subjects (20%) of the 30 treated with Zemaira® had a total of 7 exacerbations of their chronic obstructive pulmonary disease (COPD). Nine subjects (64%) of the 14 treated with Prolastin® had a total of 11 exacerbations of their COPD. The observed difference between groups was 44% (95% confidence interval from 8% to 70%). Over the entire 24-week treatment period, of the 30 subjects in the Zemaira® treatment group, 7 subjects (23%) had a total of 11 exacerbations of their COPD.

#### HOW SUPPLIED

Zemaira® is supplied in a single use vial containing the labeled amount of functionally active A<sub>1</sub>-PI, as stated on the label. Each product package (NDC 0053-7201-02) contains one single use vial of Zemaira®, one 20 mL vial of Sterile Water for Injection, USP (diluent), and one vented transfer device.

#### STORAGE

When stored up to 25°C (77°F), Zemaira® is stable for the period indicated by the expiration date on its label. Avoid freezing which may damage container for the diluent.

Prolastin® is a registered trademark of Bayer Corporation.

Revised: January, 2007

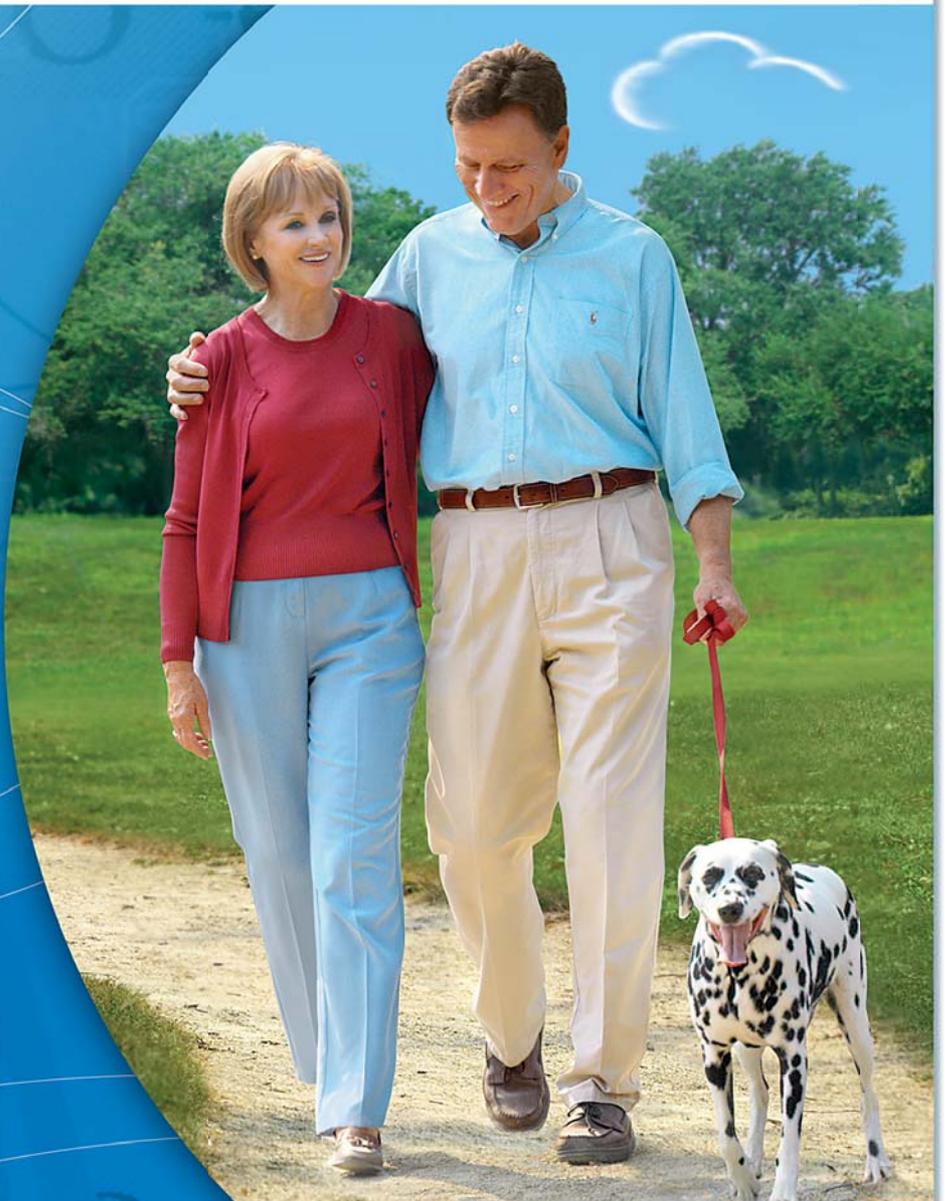
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## INDEX OF ADVERTISERS

<b>Abbott Respiratory LLC</b> Corporate	3
<b>Actelion Pharmaceuticals, Inc.</b> Tracleer	6a-6b
<b>Bryan Corporation</b> Sclerosol	8
<b>CLS Behring LLC</b> Zemaira	19-20
<b>Elan Pharmaceuticals, Inc.</b> Azactam	5-6
<b>Nationwide Medical Billing</b> Corporate	4, 14
<b>Sepracor Inc.</b> Alvesco	14a-14b, 15
<b>superDimension, Ltd.</b> inReach	11
<b>UreSil, LLC</b> TRU-CLOSE	9

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**Zemaira® — The next generation in purity for Alpha-1 augmentation therapy**

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Zemaira® is indicated for chronic augmentation and maintenance therapy for adults with alpha<sub>1</sub>-proteinase inhibitor (A<sub>1</sub>-PI) deficiency and emphysema. Clinical data demonstrating the long-term effects of chronic augmentation therapy with Zemaira® are not available.

As with other Alpha-1 therapies, Zemaira® may not be appropriate for the following adult individuals as they may experience severe reactions, including anaphylaxis: individuals with a known hypersensitivity and/or history of anaphylaxis or severe systemic reaction to A<sub>1</sub>-PI products or their components and individuals with selective IgA deficiencies who have known antibodies against IgA.

In clinical studies, the following treatment-related adverse events were reported in 1% of subjects: asthenia, injection-site pain, dizziness, headache, paresthesia, and pruritus.

Zemaira® is derived from human plasma. As with all plasma-derived products, the risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated.

For more information, call 1-866-ZEMAIRA (1-866-936-2472), or visit [www.Zemaira.com](http://www.Zemaira.com).

**References:** 1. Prolastin® Alpha<sub>1</sub>-Proteinase Inhibitor (Human), Full Prescribing Information, January 2005. 2. Aralast™ Alpha<sub>1</sub>-Proteinase Inhibitor (Human), Full Prescribing Information, August 2005. 3. Data on file, CSL Behring LLC.

**Zemaira®**  
 alpha<sub>1</sub>-proteinase inhibitor (Human)  
 Unmatched purity. Uncompromised care.

Please see brief summary of full prescribing information on following page.

\* Shelf life purity specification is  $\geq 90\%$

† In a retrospective analysis in the pivotal clinical trial, Zemaira® patients were three times less likely to experience exacerbations of their COPD than Prolastin® patients

‡ No clinically significant differences were detected between the treatment groups

§ Based on recommended dosage as stated in the product package inserts of 60 mg/kg body weight at the infusion rate of 0.08 mL/kg/min

Prolastin is a registered trademark of Talecris Biotherapeutics, Inc.