Resistant TB Strain Is Proving Deadly To HIV Patients

52 of 53 patients killed in outbreak.

BY FRAN LOWRY
Elsevier Global Medical News

TORONTO — A lethal strain of extensively drug-resistant tuberculosis (XDR-TB), which has been found to be widespread in South Africa and also is present in the United States, killed 52 of 53 patients during an outbreak in a rural South African hospital within 2 weeks of their diagnosis, said Dr. Neel R. Gandhi, formerly of Emory University, Atlanta, and now of Albert Einstein College of Medicine, N.Y.

All 53 XDR-TB patients were from KwaZulu Natal, an area of South Africa in which the TB/HIV coinfection rate is greater than 80%.

“These patients did not even appear to be terribly sick. They were not thought to be dying when they were hospitalized,” he said.

There is an epidemic of TB and HIV coinfection in South Africa, Dr. Gandhi said. Although antiretroviral therapy has significantly reduced mortality from HIV in this part of the world, drug-resistant strains of tuberculosis are negating this benefit, with 67% of deaths now attributed to multidrug-resistant (MDR) strains of TB, he said.

Dr. Gandhi and colleagues made their grim discovery after they did sputum culture and drug susceptibility testing on patients with known or suspected TB between January 2005 and March 2006. Sputum collected from 1,540 patients revealed that 536 (35%) were positive for TB. Of these, 221 patients (41%) had MDR-TB, and 53 (24%) had XDR-TB.

See Resistant • page 2

GAPP Shows Holes in Asthma Care

BY PATRICIE WENDLING
Elsevier Global Medical News

MONTREAL — There is a disconnect in communications between physicians and parents of children with asthma, according to an analysis of data from a new global asthma survey.

Parents and physicians disagree on the amount of time dedicated to asthma education in the office, who initiates discussion about medication side effects, and the level of compliance with asthma medications.

The North American pediatric findings of the Global Asthma Physician and Patient (GAPP) study also confirm what most physicians already know: Asthma medication compliance is low; patients with poor compliance experience more symptoms; and side effects lead patients to switch or drop medications.

The authors conclude that patient compliance and outcomes could be enhanced through better physician-patient communications and asthma education, and the availability of new treatment options with lower side-effect profiles, Dr. Ronald Dahl of Aarhus (Denmark) University Hospital, and his associates on the GAPP Survey Working Group reported in a poster at the Seventh International Congress on Pediatric Pulmonology.

The GAPP survey is the first ever global quantitative survey to uncover asthma attitudes and treatment practices among patients and physicians. The survey was conducted between May and August 2005 in 16 countries and included a total of 5,482 online and telephone interviews with parents and physicians.

See GAPP • page 2

Links Tighten Between Sleep Apnea and Stroke

BY SHARON WORCESTER
Elsevier Global Medical News

SALT LAKE CITY — Studies consistently show a link between obstructive sleep apnea and stroke, with the most recent data showing that sleep apnea is an independent risk factor for stroke and death.

The cumulative data in regard to sleep apnea and stroke suggest that patients with sleep apnea should be treated with continuous positive airway pressure (CPAP) or other measures, Dr. Vahid Mohsenin said at the annual meeting of the Associated Professional Sleep Societies.

The evidence supporting the efficacy of CPAP is overwhelming—with good compliance, efficacy is about 90%—and the expectation is that treatment will reduce the risk of stroke, although more research is needed to confirm this, said Dr. Mohsenin, professor of medicine and director of the Yale Center for Sleep Medicine, Yale University, New Haven, Conn.

In fact, a guideline from the American Heart Association/American Stroke Association Stroke Council for the primary prevention of ischemic stroke was updated earlier this year to incorporate new information about stroke prevention, including data on the role of sleep-disordered breathing in stroke. The guideline was initially published in 2001.

Although more research is needed, the expectation is that sleep apnea treatment will reduce stroke risk, said Dr. Vahid Mohsenin.

See Sleep Apnea • page 18

VITAL SIGNS

Number of Full-Time Physicians By Selected Specialty in 2006

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<th>Specialty</th>
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</table>

Source: Association of American Medical Colleges
Public Health Chiefs Take Aim at Drug-Resistant TB

BY JONATHAN GARDNER

The widespread infection of tuberculosis (TB) is a serious global health problem. This infectious disease affects millions of people worldwide, and a significant percentage of these cases have become resistant to the standard treatments. The emergence of drug-resistant TB (DR-TB) poses a significant challenge to public health officials, as it complicates treatment and increases the risk of transmission. The challenge is compounded by the fact that TB is often associated with HIV, which further complicates the picture.

In the recent past, there have been reports of extensively drug-resistant TB (XDR-TB), which is resistant to at least two classes of second-line drugs. This form of TB is particularly challenging to treat, and it is crucial to develop effective strategies to combat it.

The Centers for Disease Control and Prevention (CDC) have emphasized the importance of addressing this issue. They have recommended that public health authorities from 11 southern African countries should implement measures to control TB, especially in populations with high rates of HIV. The CDC has also pointed out the need for improved infection control measures, especially in healthcare settings, to prevent the transmission of XDR-TB.

In addition, the CDC has encouraged the use of vaccines to prevent the emergence of drug-resistant TB. They have highlighted the potential of vaccines in the prevention of TB and the reduction of transmission.

The XDR-TB threat is not limited to Africa; it is a global issue. The CDC has called for universal access to anti-retroviral drugs in joint TB/HIV projects.

New drugs and vaccines are on the horizon, offering hope for the future. The ongoing research into TB-resistant strains is crucial, and international public health officials are working together to address this challenge. The global community must remain vigilant and proactive in the fight against this widespread disease.
Inflammation’s Role Complicates New CF Therapies

**By Patrice Wending**

Elsvier Global Medical News

**Montréal** — A variety of new therapeutics approaches are being utilized to control airway inflammation in cystic fibrosis, but the optimal form of therapy remains to be defined. Dr. Felix Ratjen said at the Seventh International Congress on Pediatric Pulmonology.

Airway inflammation is present in most cystic fibrosis (CF) patients even before the onset of chronic infection, but it is not yet known whether this is specific to CF or related to a defect of mucus airway clearance. Two therapeutic approaches have emerged—one that directly targets inflammation and a second that addresses the underlying mucociliary clearance defect. In either case, a better understanding of the factors regulating inflammation in the CF lung is needed, because any intervention that normalizes airway inflammation may be accompanied by the detrimental effect of promoting airway infection.

“The question we really need to understand in the future is how much inflammation is needed to fight infection in CF and how much downregulation we can accept in our patients,” said Dr. Ratjen of the Hospital for Sick Children, Toronto.

Dr. Ratjen reviewed the following kinds of intervention:

- **Antibiotics** are being used to treat chronic infection, but also have been shown to have an impact on inflammation. In an induced sputum study, antibiotics significantly reduced neutrophil counts and interleukin (IL)-8 production in CF patients.
- Intravenous antibiotic therapy has been shown to significantly reduce arginine levels, which are elevated in CF patients and thought to contribute to low airway nitric oxide formation and impaired lung function (Am. J. Respir. Crit. Care Med. 2005;172:1523-8).

> “There’s some promise, but we need more data in order to see how useful this will be,” he said.

- **Oseltamivir agents** are being explored to address depletion of airway surface fluid in CF lungs that contribute to decreased airway macoelastase. So far, only hyperptonic saline has been tested. Although hypertonic saline improves lung function, it did not affect airway inflammation. The studies were relatively short in duration, and longer study is needed, he said.

- **Inhaled corticosteroids** are widely used, but so far there is no evidence that they are useful in downregulating inflammation. A recent multicenter, double-blind randomized controlled trial in the United Kingdom revealed no impact in time to first exacerbation when inhaled fluticasone was withdrawn from CF patients (Am. J. Respir. Crit. Care Med. 2006;173:1356-62).

One explanation is that inhaled steroids fail to have an impact on elastase, which is thought to be an important factor in CF lung tissue destruction, Dr. Ratjen said. Systemic corticosteroids have some anti-inflammatory effects but are not viable because of their side effects.

- **Antielastase therapy** has been shown to be safe in CF patients. But in a recent phase II study, nebulaized recombinant human α-1 antitrypsin (an inhibitor of neutrophil elastase) did not affect the amount of elastase in CF sputum samples after 4 weeks of treatment (Diatr. Pulmonol. 2006;41:177-83).

The finding may be related to dose, he said. Newer agents that are resistant to oxidation are being tested and showed promise.

- **Leukotriene B4** is important in driving neutrophils into the airways in CF. But a large phase II trial of a LTB4 receptor antagonist was stopped early due to a high rate of pulmonary exacerbations in treated patients. “This raises the question of what’s the balance of inflammation we should have in CF patients,” he said.

> “Maybe this was too effective as an anti-inflammatory agent, and if we block neutrophil influx into the lung, this may have a negative effect on patients over time.”

- **Glutathione**, a pivotal antioxidant in neutrophil production, is reduced in CF patients. A phase I study (Proc. Nail. Acad. Sci. USA 2006;103:4626-31) showed deficient glutathione levels in circulating neutrophils in CF patients, and a marked decrease in sputum elastase activity and neutrophil burden after treatment with oral N-acetylcysteine, a glutathione prodrug that has been available for years in Europe. The results are promising, but additional data are needed to confirm its benefits in CF patients, Dr. Ratjen said.

**Dr. Steven M. Rowe, MSFS, FCCP, comments:** Significant interest lies in identifying that contribute to airway inflammatory milieu of the CF lung that is generalizable to a diverse CF population and without the side effects seen with high-dose (by means of systemic) corticosteroids. Identification of an agent that is efficacious without increasing the risk of infection faces future challenges and may depend on whether the patient is irreversibly colonized with Pseudomonas or other virulent pathogens.

Low-Dose Avian Flu Vaccine Shows Preliminary Promise

**By Robert Finn**

Elsvier Global Medical News

A whole-virus vaccine for the H5N1 avian influenza virus produces acceptable levels of immunity even at low doses, researchers found in a preliminary study.

Developed at the Sinovac Biotech Co. in Beijing, the vaccine appears to be effective when delivered in two 10-mcg doses 28 days apart. A different whole-virus vaccine required two 90-mcg doses, and a split-virus vaccine required two 10-mcg doses.

Given current manufacturing constraints, supplies of that split-virus vaccine would be limited to about 225 million people, far lower than worldwide demand in the event of an avian flu pandemic.

A much greater number of people could be treated if the new dosage-sparing vaccine is found effective in larger clinical trials.

Dr. Jiaguo Lin, FCCP, of the Chinese-Japanese Friendship Hospital, Beijing, and colleagues reported on a placebo-controlled, double-blind, phase 1 trial of 120 volunteers aged 18-60 years.

The participants were given either two injections of placebo or two injections of an injected whole-virus influenza A (H5N1) vaccine. No serious adverse events were reported at any dose level up to 56 days after the first injection. Local and systemic reactions were all rated as mild and transient.

Pain at the injection site in the double-blind group was more frequent than in the placebo group, but there were no significant differences in systemic reactions, the most common of which were fever, headache, myalgia, and nausea.

In an accompanying editorial, Dr. Iain Stephenson of the Leicester (England) Royal Infirmary noted that vaccination will be central to any response to an avian flu pandemic (Lancet 2006 Sept. 7 [Epub Doi 10.1016/S0140-6736 (06)69294-5]).

> “No serious adverse events were reported at any dose level up to 56 days after the first injection. Local and systemic reactions were all rated as mild and transient. Pain at the injection site in the double-blind group was more frequent than in the placebo group, but there were no significant differences in systemic reactions, the most common of which were fever, headache, myalgia, and nausea.”

Dr. Lin could be crucial for obtaining a global supply of the vaccine.

He also noted that earlier whole-virus vaccines were associated with febrile reactions, especially in children. Although larger clinical trials will certainly be necessary before widespread immunization, Dr. Stephenson suggested that a mediator of lung reactivity might be acceptable in the face of the threat of a worldwide pandemic.

The authors of the study acknowledged that findings came from a single center, Sinovac Biotech Co., which had a role in both study design and monitoring. They said the company had no role in data collection or in writing the report.

Referral Program Cuts Waiting Times for Lung Cancer Patients

**By Doug Brunk**

CANCULAR, ALTA. — A community hospital-based virtual lung clinic staffed with a clinical navigator was able to improve waiting times from chest x-ray to diagnosis for patients with suspected lung cancer from 107 days to 31 days, Dr. Robert Zeldin reported at the annual Canadi an Society of Thoracic Surgeons meeting.

> “Fast tracking lung cancer patients does work,” said Dr. Zeldin of the division of thoracic surgery at Toronto East General Hospital.

In current practice, he said, “from the time of suspicion of lung cancer to the time of treatment, the patient journey is fragmented.”

To shorten these patients’ waiting times, Dr. Zeldin and his associates set up a virtual lung clinic, which involved the referring primary care physicians, hospital-based specialists, and a regional cancer center. The goal was to get a patient with suspected lung cancer referred to a respiriologist or thoracic surgeon within 3 working days.

The investigators hired a clerical navigator to answer what they called a “lung hotline” and to process forms they created for referring primary physicians. That way, Dr. Zeldin said, “when a patient comes in with either a suspected symptom of lung cancer or a suspicious chest x-ray, then it becomes an easy method of referral for the family doctor. They are directed on the form to schedule with the appropriate specialist.”

The clerical navigator also booked CT scans as indicated. A tumor board consisting of two thoracic surgeons and three radiologists oversaw the coordination of care.

Over a 3-month period, the researchers compared waiting time intervals between chest x-ray and diagnosis from a group of 52 historical controls and a group of 61 patients who participated in the new referral program. The wait times improved dramatically, from a mean of 107 days in the control group to a mean of 31 days in the referral program patients.

Dr. Beldin said that a larger study is underway to determine the impact of the referral program on disease staging at time of diagnosis and subsequent treatment. Cancer Center Ontario and the Ontario Ministry of Health and Long-Term Care funded the study.

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**New Options Taking Shape in TB Diagnostic Testing**

**BY BRUCE JANCIN**

Better diagnostic tests are seen as essential in the campaign to control the global tuberculosis epidemic—and help is on the way.

The archaic, nearly 100-year-old tuberculin skin test was until recently the sole tool available for diagnosis of latent TB infection. The skin test has several limitations, chiefly its low specificity due to cross-reactivity with the BCG vaccine and false-positives in persons infected with non-TB mycobacteria, Dr. Karin Weldingh said at the 12th International Congress on Infectious Diseases.

Major international aid organizations including the Foundation for Innovative New Diagnostics, the Stop TB Partnership, and the World Health Organization have declared development of faster, simpler, more convenient, and more accurate TB diagnostic tests to be a high priority.

Recently, two novel cell-mediated immune response–based assays have become widely commercially available as alternatives to the skin test for detection of latent TB. The in vitro assays—the QuantiFERON-TB Gold and T-SPOT.TB assay—measure interferon-γ released by sensitized T cells following stimulation by antigens specific to Mycobacterium tuberculosis, including culture filtrate protein-10 (CFP-10) and early secreted antigenic target-6 (ESAT-6).

Studies show these assay kits have better specificity for detection of latent TB and are at least as sensitive as the skin test for active TB; plus, they’re interpreted more objectively, with results available in a day, said Dr. Weldingh of the Statens Serum Institute, Copenhagen.

The QuantiFERON-TB Gold assay was first to win approval by the Food and Drug Administration. Late in 2005, the Centers for Disease Control and Prevention recommended its use in all situations where the skin test has been used.

The downsides of using these assays in the developing world are that they require living cells and ready access to a lab for enzyme-linked immunosorbent assay. “This means you have to process blood samples within 12 hours,” she explained at the congress sponsored by the International Society for Infectious Diseases.

Dr. Weldingh sees the assays ultimately being most useful for latent TB case finding via contact tracing and screening of high-risk groups in low-endemic, highly developed areas such as Western Europe and the United States. The tests should prove useful in areas with an intermediate TB incidence and good infrastructure, such as parts of Brazil.

In places where TB rates are high, roads poor, and laboratories hard to come by, these tests aren’t practical. The solution in such places is probably an improved skin test that utilizes M. tuberculosis-specific antigens rather than the traditional purified protein derivative; such tests are now under evaluation in field studies.

Another approach involves serologic antibody tests. These are much less temperature-sensitive and fragile than the interferon-γ tests, they don’t require living cells or access to a laboratory, and they yield results in 15-30 minutes.

The newer ones, which utilize M. tuberculosis-specific antigens, perform best. They’ll never serve as a stand-alone test for diagnosis of active TB, but they could have a role as rule-in screening tests that trigger definitive testing, she said.

**XOLAIR IS INDICATED FOR:**

Adults and adolescents (aged ≥12 years) with moderate- to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial allergen and whose symptoms are inadequately controlled with inhaled corticosteroids. XOLAIR has been shown to decrease the incidence of asthma exacerbations in these patients. Safety and efficacy have not been established in other allergic conditions.

**IMPORTANT SAFETY INFORMATION**

XOLAIR should not be administered to patients who have experienced a severe hypersensitivity reaction to XOLAIR.

The most serious adverse events occurring in clinical studies with XOLAIR were malignancies and anaphylaxis. Malignant neoplasms were observed in 0.5% of patients treated with XOLAIR compared with 0.2% of control patients in clinical studies. The observed malignancies in patients treated with XOLAIR were a variety of types, with breast, nonmelanoma skin, prostate, melanoma, and parotid occurring more than once, and 5 other types occurring once each. The majority of patients were observed for less than 1 year. The impact of longer exposure to XOLAIR or use in patients at higher risk of malignancy is unknown.

Anaphylaxis has occurred within 2 hours of the first or subsequent administration of XOLAIR in <0.1% of patients without other identifiable allergic triggers. Anaphylactic reactions were rare but temporally associated with XOLAIR administration. Patients should be observed after injection of XOLAIR, and medications for the treatment of severe hypersensitivity reactions, including anaphylaxis, should be available. If a severe hypersensitivity reaction to XOLAIR occurs, therapy should be discontinued.

XOLAIR has not been shown to alleviate asthma exacerbations acutely and should not be used for the treatment of acute bronchospasm or status asthmaticus.

Systemic or inhaled corticosteroids should not be abruptly discontinued upon initiation of XOLAIR therapy. Decreases in corticosteroids should be performed only under the direct supervision of a physician and may need to be performed gradually.

In clinical trials, the most frequent adverse events included injection-site reaction (45%), viral infections (23%), upper respiratory tract infection (20%), sinusitis (7%), headache (15%), and pharyngitis (11%). These events were observed at similar rates in patients treated with XOLAIR and control patients.

**References:**


Genentech | Novartis
89301:00 X01-1023 9/06 Printed in USA
Several generic versions of the intravenous formulation of the widely used fluoroquinolone ciprofloxacin have been approved by the Food and Drug Administration, as part of what the agency says is its effort to make lower-cost generic drugs more widely available.

The generic formulations are versions of the trade formulation of CIPRO IV, approved in 1991 and marketed by Bayer Corp. Ciprofloxacin injection is provided in a concentration of 10 mg/mL, and is packaged in 20 mL and 40 mL vials, and in a 120 mL pharmacy bulk package, according to a statement issued Aug. 28 by the FDA to announce the approval. Drug Topics, an online magazine, listed Cipro IV injection as the top-selling drug in its list of the 200 highest-selling brand name drugs in the United States in 2005, according to the statement. The wholesale acquisition cost of the drugs used in hospitals totaled $115,333,072.

Ciprofloxacin injection is approved for treating infections caused by susceptible strains of designated microorganisms for certain infections in adults, including urinary tract infections, lower respiratory tract infections, nosocomial pneumonia, bone and joint infections, complicated intraabdominal infections, skin and skin structure infections, acute sinusitis, and empirical therapy in febrile patients with neutropenia. It is approved for treating complicated UTIs and pyelonephritis due to *Escherichia coli*, in patients aged 1-17 years, but not as a first choice, according to the CIPRO IV label. It is also approved to reduce the incidence of inhalational anthrax after exposure to aerosolized *Bacillus anthracis* in adult and pediatric patients. The approval of these generic versions of ciprofloxacin injection “can bring significant savings to the millions of Americans who have certain bacterial infections that can be treated with ciprofloxacin,” Gary J. Buehler, a pharmacist and director of the FDA’s Office of Generic Drugs, said in the FDA statement.

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**FDA Approves Generic Forms of IV Ciprofloxacin**

She has IgE-mediated asthma... Don’t just get her up, get her out

Only XOALAIR inhibits IgE to help protect patients against asthma exacerbations and symptoms.

When ICS aren’t enough, add XOALAIR to help:

- Reduce exacerbations1 and symptoms to help prevent asthma from disrupting daily routine activities
- Reduce nighttime awakenings
- Reduce daytime symptoms such as wheezing and coughing

More than 60,000 prescriptions since launch.1

1Inhaled corticosteroids.

1An asthma exacerbation was defined as a worsening of asthma that required treatment with systemic corticosteroids or a doubling of the subjects baseline beclomethasone dipropionate dose.

Please see following page for brief summary of the Full Prescribing Information.
ELECTIVE PNEUMONECTOMY MAY LEAD TO LOW MORTALITY

BY DOUG BRUNK
Elsevier Global Medical News

C A L G A R Y , A L T A . — Elective pneumonectomies carry a low mortality rate and result in shorter hospital stays, according to a long-term study carried out at a high-volume regional academic medical center for thoracic surgery.

However, more complicated pneumonectomies may carry an increased risk of death or clinical problems, Jennifer Rattenbury reported at the annual Canadian Surgery Forum. The finding is important because although the medical literature is replete with cases of pneumonectomies, “there are a range of higher rates of complications and a higher mortality rate,” said Ms. Rattenbury, who is a clinical research coordinator with the division of thoracic surgery at the University of British Columbia, Vancouver.

It is compounded by the fact that in recent years the patient base [for the procedure] is broadening to patients that are older and have more comorbid diseases,” as well as those who have undergone neoadjuvant therapy.

In the medical literature, she added, the mortality rates for pneumonectomy range from 0% to 25%, but generally stand at 10%. The complication rates vary between 15% and 43%.

She and her associates reviewed the records of 128 patients with a mean age of 61 years who underwent an elective pneumonectomy at Vancouver General Hospital between March 2001 and January 2006. More than half (69) of the patients were male and 67 of the procedures were left sided. A total of 85 of the procedures were simple pneumonectomies, and 43 were complex.

Of the 128 patients, 111 (87%) had no complications while 40% had one or more complications. Overall, 20% of the complications were considered to be minor, including pleural effusion, other postoperative respiratory problems, pulmonary edema, and pneumoniectomy.

Dr. Robert J. Cerfolio, FCCP, comments: Although pneumonectomy has increased risk when compared to other types of elective pulmonary resection, if it is the only operation possible that achieves a complete margin negative resection, then it remains a viable option for the patient with non–small cell lung cancer.
Necrotizing Pneumonia Rises in Pediatric Cases

BY PATRICE WENDLING
Elsevier Global Medical News

MONTREAL — Necrotizing pneumonia is a more common complication of community-acquired pediatric pneumonia than was previously appreciated, Dr. Gregory Sawicki and associates reported at the Seventh International Congress on Pediatric Pulmonology.

An analysis of 80 cases at Children’s Hospital Boston identified a rise in cases from 12 during 1993-1996 to 29 in 2003-2003, and a troubling increase in new pathogens.

“Though pneumococcus was the prevailing pathogen, we observed a rising trend of different causative microorganisms, including MRSA [methicillin-resistant Staphylococcus aureus],” said Dr. Sawicki of the hospital’s division of respiratory diseases.

Despite the serious morbidity, mortality, and increased parenchymal damage, and prolonged hospitalizations, treatment options are limited, the study’s authors said.

The cases were retrospectively identified from a database of CT scans spanning January 1993 to February 2005, followed by a full chart review.

To varying degrees, all cases had large areas of decreased parenchymal enhancement and loss of normal lung parenchymal architecture, with multiple thin-walled and fluid-filled cavities.

Nosocomial and significant complications included pleural effusion, alveolar decortication in 3 patients (4%); and open thoracotomy/pleural decortication in 3 patients (59%); chest tube and surgery in 25 (32%) who needed extracorporeal circulation membrane oxygenation, 25 (32%) who needed ICU care, and 8 (10%) who were discharged at a median of 6 months.

In the series, conservative management with chest drainage alone resulted in outcomes similar to those of surgical management, with no significant differences reported in length of hospital stay, length of fever, or length of pleural fluid drainage, Dr. Sawicki reported.

Overall complications included 10 patients (13%) who developed a bronchopleural fistula, 1 who needed extracorporeal circulation membrane oxygenation, 25 (32%) who needed ICU care, and 8 (10%) who were readmitted.

All 63 patients seen post discharge at a median of 6 months had clinical resolution of symptoms within 2 months.

Audience members questioned whether necrotizing pneumonia is really increasing or whether identification has become more frequent with the use of CT scans. That question could not be definitely answered by the study, Dr. Sawicki said. However, the number of scans for a diagnosis of pneumonia has increased at his institution, he noted.

Preterm Birth and Small Size Have Lasting Effect on Lungs

BY PATRICE WENDLING
Elsevier Global Medical News

MONTREAL — The first long-term follow-up of infants with bronchopulmonary dysplasia suggests that the consequences of being born too small, but not prematurity, are similar effects observed in preterm survivors.

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The cases were retrospectively identified from a database of CT scans spanning January 1993 to February 2005, followed by a full chart review.

To varying degrees, all cases had large areas of decreased parenchymal enhancement and loss of normal lung parenchymal architecture, with multiple thin-walled and fluid-filled cavities.

Nosocomial and significant complications included pleural effusion, alveolar decortication in 3 patients (4%); and open thoracotomy/pleural decortication in 3 patients (59%); chest tube and surgery in 25 (32%) who needed extracorporeal circulation membrane oxygenation, 25 (32%) who needed ICU care, and 8 (10%) who were discharged at a median of 6 months.

In the series, conservative management with chest drainage alone resulted in outcomes similar to those of surgical management, with no significant differences reported in length of hospital stay, length of fever, or length of pleural fluid drainage, Dr. Sawicki reported.

Overall complications included 10 patients (13%) who developed a bronchopleural fistula, 1 who needed extracorporeal circulation membrane oxygenation, 25 (32%) who needed ICU care, and 8 (10%) who were readmitted.

All 63 patients seen post discharge at a median of 6 months had clinical resolution of symptoms within 2 months.

Audience members questioned whether necrotizing pneumonia is really increasing or whether identification has become more frequent with the use of CT scans. That question could not be definitely answered by the study, Dr. Sawicki said. However, the number of scans for a diagnosis of pneumonia has increased at his institution, he noted.
PCHEST PHYSICIAN • OCTOBER 2006

NEWS FROM THE COLLEGE

PRESIDENT’S REPORT
My Final Column

I have just returned from the ACCP Pulmonary Board Review Course in Orlando. As it is just “down the street” from Tampa, I drove over, gave three lectures, and dropped by the office on my way home to “put out a few fires” and commit my editorial thoughts to paper, before taking off tomorrow for the European Respiratory Society meeting in Munich. The triple ACCP board review courses (sleep medicine, critical care medicine, and pulmonary, all held at the Dolphin Resort at Disney World, one after another) were outstanding and extremely well attended. The College does many great things, and the board review courses rank near the top.

This President’s Report is bittersweet, as it will be my final column as a sitting President. The year has literally flown by. As advised by one of my predecessors, the year will be challenging and exhausting but the most professionally rewarding of your career. As the end of my term approaches, I find that I could not agree with him more.

During my presidential report at the Board of Regents meeting in July, I estimated that when averaged over the year, I would spend 3 hours per day on College business, whether that be brainstorming with Al Lever on the phone, preparing for the Executive Committee conference calls, answering e-mails, or any of a myriad of other tasks.

Yet, the work did not seem onerous, as 99% of the presidential duties were rewarding and satisfying and advanced the College’s vision and mission. While I have the floor and your attention, let me thank some very special people. First and foremost, I would like to thank my wife Debra, my daughter Katie, and my son Michael. I sincerely appreciate their support and patience during the year. At times, Debra was busier than I with College business in her role as Chair of the Ambassadors Group. I am extremely proud of her accomplishments in this position. I would also like to thank the University of South Florida College of Medicine and the Moffitt Cancer Center for permitting me to serve in this presidential role. I would like to thank Al Lever and the entire ACCP and CHEST Foundation staff. After working so closely with this group for the past year, I feel qualified to reiterate that we have the best in the business working with us.

Thanks is also due any number of other individuals, including the Executive Committee, the Board of Regents, the Governors, the NetWork Chairs, the Committee Chairs, and on and on. The College is blessed with many talented and committed individuals who share in the ACCP mission and vision.

Let me close by thanking you, the membership of the ACCP, for affording me the privilege of serving as your President. It is an honor that I will forever cherish. I leave the presidency in good hands and the College in great shape, both financially and organizationally. There are challenges looming but nothing that ACCP CEO and Executive Vice President Al Lever, President-Elect Mark Rosen, President-Designate Al Thomas, and the entire ACCP family can’t handle.

CHEST Foundation Presents Tobacco Education Panel

The CHEST Foundation presented its tobacco educational work at the 13th World Conference on Tobacco OR Health, July 12-15, 2006, in Washington, DC. This meeting is held every 4 years with heavy participation from WHO, CDC, and a number of international organizations. The 90-minute symposium/panel on “Tobacco Education in Women: International Tools,” in which the CHEST Foundation participated, was moderated by Dr. Terry Fonfam.

Dr. Deborah Shure, Master FCCP and Past President of ACCP started the panel and spoke about the evolution and the history of The CHEST Foundation and its focus on tobacco prevention that is particularly geared to women and girls. Dr. Kay Guntupalli, FCCP, past Trustee of The CHEST Foundation, followed and spoke about the development of age and culturally specific tools for children globally and for the Indian subcontinent. She shared details on the development, evaluation, and impact of tools that she has developed for The CHEST Foundation. Dr. Judith Mackay, past honoree of The CHEST Foundation and the ACCP, presented the adaptation of the USA kit for the Asian countries that she developed for The CHEST Foundation. A lively, interactive discussion followed. CHEST Foundation CDs of many of its tobacco education tools were distributed to the attendees. Dr. Robert McCaffree, Master FCCP and Past President of ACCP and current President of The CHEST Foundation, and Dr. Mary Anne McCaffree, active participants in the development and implementation of these programs, also added input during the discussion.

Dr. Kay Guntupalli, FCCP: “This was a great opportunity to showcase the tools developed by The CHEST Foundation. The response and interest from the packed audience was very gratifying. It emphasizes the need for continued work in this area.”

Dr. Deborah Shure, Master FCCP: “This was a lively, international session with great interest expressed in the use of CHEST Foundation speakers kits and educational material on tobacco control. Many participants shared their experiences and ideas for further adaptations. The impact of The CHEST Foundation’s involvement in this area is truly significant and appreciated.”

Dr. D. Robert McCaffree, Master FCCP: “This World Congress reinvigorated our total antipathy toward the tobacco industry, which is engineering the greatest pandemic the world has seen—a pandemic that is killing 5 million people annually now and will soon be killing 20 million people worldwide. It is always inspiring to be with people strongly committed to fighting tobacco and sharing ideas of ways to protect our youth and our communities.”
News from the College

BY JENNIFER STAWARZ
Senior Manager, ACCP Public Relations

Studies published in the journal CHEST have kept the American College of Chest Physicians in the spotlight throughout the summer. In early May, a study illustrating the gender differences associated with lung cancer gained coverage in the Washington Post, Los Angeles Times, The Tennessean, and The Vancouver Sun. The study was also featured in nearly 50 television broadcasts in such markets as Los Angeles, Detroit, Philadelphia, Baltimore, and on MSNBC Live.

In late May, the Health Resources and Services Administration (HRSA) submitted a report to the US Department of Health and Human Services regarding the critical care workforce shortage. In response, the ACCP and other specialty medical societies distributed a joint press release outlining the findings of the HRSA report and potential solutions for the shortage of critical care workers. As a result, the Associated Press published a story regarding the critical care workforce shortage, which, subsequently, ran on numerous consumer and medical Web sites and television stations around the country.

In June and July, ACCP evidence-based guidelines for antithrombotic therapy (September 2004) were mentioned in the Canadian Pharmacists Journal and Washington Pharmacy magazine. The ACCP guidelines for atrial fibrillation (August 2005) were also featured in The Medical Post, Emergency Medicine, and Drug Topics. Additional CHEST studies were featured in the Baltimore Sun, Hartford Courant, Dayton Daily News, Hospital Pharmacy, Vitality, Women’s Health Magazine, and CNN and CBS news online. Access ACCP press releases at www.chestnet.org/about/news.php.

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ACCP in the News

Lung Cancer Alliance Is Committed to Patient Education

The Lung Cancer Alliance (LCA) is the only national nonprofit organization providing patient support and advocacy exclusive to those living with or at risk for lung cancer. Headquartered in Washington, DC, LCA is committed to making lung cancer a national public health priority.

Through a hotline (800-298-2436) and a Phone Buddy Program, one-on-one support to people affected by lung cancer is delivered. The Hotline receives 450 to 500 calls per month from all over the United States. The Phone Buddy program is a peer-to-peer support network made up of 150 survivors and caregivers who have volunteered to share their experiences and be empathetic listeners. LCA makes approximately 40 matches per month between volunteers and those in need. Phone Buddies do not give medical advice. Volunteers receive ongoing training and support. This is the only peer-to-peer national resource specific to lung cancer.

LCA provides not only one-on-one support but is building a community of people to support each other and a movement to make lung cancer a national public health priority. This is done through programs, publications, and communications. LCA hosts a blog www.lungcancerallianceblog.org, and an online support community. The LCA Survivors Community is a safe, trusted environment in which those at risk, those living with the disease, and those who love them can share and support one another.

An additional resource for patients is the LCA Clinical Trials Matching Service. The Service ensures that patients diagnosed with lung cancer know all of their treatment options, including clinical trials.

Physicians’ offices can receive sets of brochures about LCA services for patients and family members, so they have a place to turn for support and education. The quarterly Spirit & Breath newsletter shares information on congressional and executive branch news relevant to lung cancer, as does the LCA Web site at www.lungcanceralliance.org.

■

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ACCP Worldwide

11th Congress of the Asian Pacific Society of Respirology
November 19–22, 2006
Kyoto, Japan

The main theme of the APSR 2006 is “New Horizons of Respirology—Harmonization Beyond Diversity.”

The President of the 11th Congress, Dr. Yoshinori Fukuchi, FCCP, remarks that some of the meeting highlights include a satellite symposium in Tokyo on respiratory physiology; a special seminar on the creation of scientific papers (with a faculty of the Editors in Chief of APSR, ACCP, ATS, and ERS); a symposium on GOLD revision 2006 (featuring six Executive Members), and many more symposia/seminars embracing major respiratory diseases common to that part of the world.

Leaders from the ACCP will be participating in several special sessions.


World Asthma Meeting (WAM) 2007
June 22-25, 2007
Istanbul, Turkey

The theme of WAM 2007 is “Bridging Various Aspects of Asthma.” Professor Eldif Daghi, Chair of the WAM Committee, notes, “The WAM Committee wished to discuss regional perspectives of asthma in a city on two different continents, historically and geographically connecting Northern Africa, Middle East, Central Asia, and East Europe. Please come and let yourself be spoiled with the famous Turkish hospitality.” The scientific program will include postgraduate courses, keynote lectures, plenary sessions, symposia, and hot topic sessions on obesity and asthma, severity vs control, new insights in immunopathogenesis, and safety of LABAs. The ACCP serves on the WAM 2007 Committee, and ACCP members will be participating in the program.

More information is available at www.wam2007.org/.

November Is Lung Cancer Awareness Month

November 16 is the Great American Smokeout

Tools and resources related to lung cancer are available for download or purchase.

Learn more at www.chestnet.org/lungcancer.

E D U C A T I O N I N S I G H T S

The Transformation of Medical Education

BY ED DELLERT, RN, MBA
Vice President,
ACCP Educational Resources

Most models of medical education are based upon the content of the curriculum, the organization of the teaching, assessment of the learner, and the evaluation of the educational program. Over the last several years, there have been concerns raised about the educational impact as to how teachers are helping learners obtain the information they really want them to know.

Much is at stake, including the effectiveness of the education program to the careers of the individual students.

This spills over into what students will take with them and practice throughout their career as they continue their medical education efforts.

How serious is this to the future of medical education and continuing medical education providers? If one were to ask me, I would respond that change in medical education is inevitable. This opinion is based upon three sources of information:

1. American Medical Association (AMA) Initiative to Transform Medical Education;
2. Prior publications to change the CME credit system; and
3. The September 2006 release of new Accreditation Council for Continuing Medical Education (ACME) criteria.

A recent report from the AMA highlights the work of a committee called the “Initiative to Transform Medical Education” (ITME) that indicates its goal as follows:

“Our AMA should assume a leadership role in creating the forums, strategies, and structures appropriate for reforming the American Medical Education system across the continuum of education and professional training to enable physicians to meet the needs of patients and the public through the health-care delivery system in the twenty-first century.”

The ITME is scheduled to make recommendations to the AMA by the end of the 2006 calendar year on how best to change the continuum of medical education, factors that will facilitate or inhibit the implementation of such a change, and assuring that appropriate groups and organizations are supportive of these proposed recommendations.

As for continuing medical education (CME) credit, the current time-based system has assumed that awarding such credit would lead toward a change in physician behavior and improved patient care. Physician participation in CME activities and its correlation to this desired change has been a subject of debate with results that are sporadic, at best.

This was highlighted by an article by Nancy Davis and Charles Willis (2004, The Journal of Continuing Education in the Health Professions). It indicated that a new CME system needs to focus on the value of an educational activity that is measured by improved physician performance and not by time.

To CME providers and educators, this means change to the structure of future educational programs.

On September 5, 2006, the ACCME published updated criteria for CME providers to implement in stages between November 2008 and November 2012. The focus of the ACCME updated elements is on enhancements to CME programs through their mission statement and assessing how they achieve their mission, concentrating on the impact of their educational activities upon physician performance-in-practice or patient outcomes.

Change in medical education and how physicians participate in these educational activities is altering. These models described in this article only highlight that change appears to be on the horizon and that change will include demonstrating how knowledge, competence, or performance was improved based upon participation in high-quality educational designs and programs.

References

A NEW CME SYSTEM NEEDS TO FOCUS ON THE VALUE OF AN EDUCATIONAL ACTIVITY THAT IS MEASURED BY IMPROVED PERFORMANCE AND NOT BY TIME.
Pain management: The need for a systematic approach

In recent years, great attention has been paid to detecting and documenting pain that is experienced by any patient. Typically, detection relies upon self-reporting by a coherent, conscious patient. This is often in the form of identifying a level of pain using a 10-point numeric scale and may incorporate cartoons of faces varying from happy to frowning. ICU patients present unique challenges for this form of assessment, because many have impaired levels of consciousness and/or reduced ability to communicate. The scheduled interruption of sedative medications, often performed on a daily basis (Kress et al. N Engl J Med 2000; 342:1472), presents an opportunity for care providers to inquire about pain during this period of relative alertness.

When a practitioner is unable to solicit a description of the pain or its rating, then the presence or absence of pain is often inferred by care providers based upon observed behaviors and changes in vital signs. An ICU study of nearly 6,000 ICU patients, Puntillo and colleagues noted certain facial, body movement, and verbal behaviors to be associated with pain induced by various procedures (Puntillo et al. Crit Care Med 2004; 32:421). Grimacing, a rigid body position, wincing, and eye closure were among the most often observed behaviors. Activation of the sympathetic nervous system is common during pain and often results in tachycardia, tachypnea, hypertension, and papillary dilatation. However, changes in these parameters have not proven to be reliable reflections of presence or absence of pain, because many other conditions stimulate sympathetic discharge and the stress response. In addition, many medications can blunt the sympathetic response, whereas, others will further stimulate the sympathetic nervous system.

Self-reporting of pain is often difficult to achieve among ICU patients, so clinicians and investigators have sought to develop valid instruments to detect and, perhaps, quantify pain. In the 12-point Behavioral Pain Scale (BPS) (Payen et al. Crit Care Med 2001; 29:2258), facial expressions and upper limb posture are two of the three domains (compliance with ventilation is the third) that are used to determine the presence and severity of pain in patients who are nonverbal. As a form of validation, the authors observed an increase in BPS with noxious procedures, compared with nonnoxious procedures. However, changes in the scale were most reliable during light sedation, however, and was not particularly robust for detecting pain when deep sedation was present. Blenkharn and colleagues (Blenkharn et al. Intensive Care Nursing 2002; 18:332) developed the Observational Pain Scoring Tool that incorporates hypertension, tachycardia, sweating, papillary dilatation, facial grimacing, and distressed movements into a rating of zero to three points that is utilized in a management protocol. An attractive feature of the proposed management strategy is that self-reporting of pain by the alert patient is utilized first to guide treatment. The downside to implementing this as a unit-wide tool is that these authors did not prospectively validate this management algorithm. Chanques and colleagues (Chanques et al. Crit Care Med 2006; 34:1691) tested the impact of a systematic management strategy for pain and agitation and demonstrated impressive results. They utilized a numerical rating scale and the BPS for pain evaluation and the Richmond Agitation-Sedation Scale for agitation. The protocol lists specific actions to be taken by the clinician in response to detecting pain or agitation and includes a search for underlying conditions that might be corrected and the selection of an appropriate analgesic agent based upon World Health Organization classification. This matches specific medications with pain severity. In a two-phase, prospective, controlled study, this strategy led to more therapeutic changes—both escalation and de-escalation of therapy—and was associated with a significant reduction in the incidence of pain and agitation. The intervention was associated with shorter duration of mechanical ventilation and fewer nosocomial infections. The ICU length of stay and survival remained unchanged.

Analogic medications are widely prescribed in the ICU setting to treat or manage pain. Opioids were administered on 34% of days in a large cohort of mechanically ventilated ICU patients (Arroliga et al. Chest 2005; 128:496). Although these drugs were used in a targeted fashion to treat pain, particularly by intermittent administration, they are also widely used in sedation management, often by continuous infusion, within the context of “analgesic sparing.” In support of this practice, a combination of a benzodiazepine and opiate infusion has been suggested to be more reliable and easier to titrate than benzodiazepine infusion alone (Richman et al. Crit Care Med 1996; 14:195), even for patients without a recognized need for pain relief.

Because of the complexity of pain management in ICUs, there is a need for more widespread adoption of a systematic approach to evaluating and managing pain in ICUs.

Some of the work discussed provides a starting point, with regard specifically to utilization of tools for detecting and documenting pain. Additionally, a framework for development of management strategies is an area for more research.

There are important aspects of pain management for which clear gaps exist, including a research basis for management, dissemination of information, and an incorporation of this knowledge into daily clinical care. Pain recognition in the nonverbal patient, individualized analgesic drug selection and dosing, management of GI hypomotility related to opioid analogues, and nonpharmacologic strategies for easing discomfort or preventing pain are examples of common issues that the critical care community must address.

There are certain aspects of pain management that present unique challenges. For example, neuropathic pain is underappreciated as a cause of pain, and nontraditional management options, such as anticonvulsants, antiarhythmic, local anesthetics, and antidepressants may be more effective than opioids, and antiinflammatory, yet, are often not considered. The role of central neuroaxis drug administration also must be examined. Last, symptom relief, particularly the elimination of pain in end-of-life situations, is a crucial issue and must be addressed by the critical care team.

With support from the ACCP Critical Care Institute and the American Association of Critical-Care Nurses, an expert panel has been convened to address these many issues, with the goal of eliminating “unmanaged” pain in the ICU.
Pleurodesis is indicated for the treatment of malignant pleural effusion, spontaneous pneumothorax, and selected cases of benign pleural effusion. Although a number of agents have been used for pleurodesis, talc is the most effective. In addition to achieving pleurodesis, talc also induces apoptosis in malignant mesothelial cells but not in normal pleural mesothelial cells, even at a dose less than one hundredth of that used in pleurodesis (Najmunnisa et al. Am J Respir Crit Care Med 2000; 161:959).

Variable Physical Properties of Talc
Talc is a pulverized form of a naturally occurring hydrated magnesium silicate with variable amounts of aluminum, iron, or manganese. In nature, talc is not found in a chemically pure state. It may be contaminated by other minerals, including asbestos, although medical grade talc is asbestos-free. There is marked variation in the diameter of talc particles. In one study of preparations from various countries, the median diameter varied from 7.8 µm to 31.3 µm, while 10th percentile diameters were as low as 2.4 µm, and 90th percentile diameters were as high as 60.6 µm (Ferrer et al. Chest 2001; 119:1901). Preparations from the United States had the smallest particle size.

Mechanisms of Pleurodesis
Talc pleurodesis causes injury to the pleural mesothelium, followed by inflammation and fibrosis. The injury is mediated by pleural mesothelial cell production of interleukin-8, monocyte chemotactic protein-1, intercellular adhesion molecule-1, and basic fibroblast growth factor (Najmunnisa et al. Am J Respir Crit Care Med 1998; 158:971). Intrapleural instillation of talc is rapidly followed by influx of neutrophils and subsequent accumulation of macrophages. A decrease in pleural fibrinolytic activity also occurs.

Talc and ARDS
A lingering concern about the use of talc is the occurrence of ARDS after talc pleurodesis. Talc. The reported incidence of post-talc ARDS in large, observational studies varies from 0 to 9% (Kennedy et al. Chest 1994; 106:342; Campos and Werbe. Lancet 1997; 349:251; Rehse et al. Am J Surg 1999; 177:437). A causal relationship between extrapleural dissemination of talc and the occurrence of ARDS has been suggested by the finding of talc particles in the BAL fluid of patients with post-talc ARDS (Campos and Werbe. Lancet 1997; 349:251), lending additional support to the role of extrapleural dissemination in the pathogenesis of post-talc ARDS. The influences of talc size and dose have been investigated as factors in dissemination.

Talc Size
ARDS is more common in the United States, where talc particles are smaller, suggesting an association between particle size and the risk of ARDS. Further support for this association is found in a study of the use of facial talc, with a relatively larger particle size, vs medical grade talc, with a relatively smaller particle size. No cases of ARDS occurred with the use of sterilized facial talc for pleurodesis (Khoja et al. J Bronchol 2004; 11:226).

A rabbit model of talc slurry pleurodesis using smaller or larger talc particles provided further evidence of the importance of talc particle diameter in dissemination. Smaller and larger talc particle slurry achieved equivalent pleurodesis, but smaller talc particle slurry caused more deposition of talc particles in the ipsilateral lung and other organs. Talc reached the lung parenchyma by disrupting the integrity of the mesothelium and the elastic layer. Aggregates of talc particles accumulated mainly in the periphery of the lung parenchyma, but some talc particles followed the bronchovascular spaces to reach small blood and lymphatic vessels (Ferrer et al. Chest 2002; 122:1018).

Definitive evidence of the clinical importance of talc particle size comes from a prospective, randomized trial of talc slurry pleurodesis using samples of differing particle size in 48 patients. The slurries with smaller talc particles caused greater increases in alveolar-arterial oxygen gradient, greater decreases in arterial oxygen tension, and greater increases in plasma C-reactive protein level. Pleurodesis was similarly successful in both groups among survivors at 3 months (Maskell et al. Am J Respir Crit Care Med 2004; 170:377).

Talc Dose
Most cases of post-talc pleurodesis ARDS have occurred with high doses of talc. In one report, three cases of ARDS were found after talc pleurodesis for malignant effusions using 10 g of talc (Rinaldo et al. J Thorac Cardiovasc Surg 1983; 85:523). In another series of 78 patients undergoing pleurodesis for recurrent effusion or pneumothorax, 7 patients (9%) developed ARDS. All of the patients who developed ARDS had received a talc dose of 5 g (Rehse et al. Am J Surg 1999; 177:437). These observations suggest that extrapleural dissemination of talc is a dose-dependent phenomenon.

The dose-dependent hypothesis was tested in a rabbit model of talc slurry pleurodesis (Montes et al. Am J Respir Crit Care Med 2003; 163:348). Rabbits in the high-dose group were more likely to have talc deposition in the ipsilateral and contralateral lung, mediastinum, pericardium, and liver, compared with rabbits in the low-dose group.

Methods of Sterilization and Delivery
Talc may be sterilized effectively by dry heat, gamma irradiation, or ethylene oxide gas, although dry heat is the least expensive method (Kennedy et al. Chest 1995; 107:1032).

Intrapleural instillation of talc slurry via a chest tube and thoracoscopic talc poudrage are similarly effective in achieving pleurodesis (Kennedy and Sahm. Chest 1994; 106:1215; Dresler et al. Chest 2003; 127:909). In a slurry, the talc particles tend to aggregate. After instillation in the pleural space, aggregates of talc particles may quickly gravitate to, and accumulate in, the dependent part of the pleural space. Thoracoscopic talc poudrage may be done in an operating department or endoscopically. In either case, thoracoscopic talc poudrage is a more expensive procedure than intrapleural instillation of talc slurry via a chest tube. Pleurodesis with thoracoscopic talc poudrage may result in a shorter duration (4.4 days) of chest tube drainage, compared with talc slurry (Aelony et al. Ann Int Med 1991; 115:778).

Dr. Deborah Shure, Master FCCP
Editor, Pulmonary Perspectives
Dr. Aymarah Robles, FCCP
Deputy Editor, Pulmonary Perspectives

A BASIC CONCLUSION IS THAT THE RISK OF SEVERE SYSTEMIC INFLAMMATION AND ARDS WILL BE DECREased BY THE USE OF TALC PREPARATIONS WITHOUT SMALL PARTICLES.
The CHEST 2007 Scientific Program Committee wants your ideas for topic presentations at CHEST 2007. Help make this meeting a valuable learning experience by submitting your ideas for session topics today.

Topic submission will begin late in September. Submit your ideas online at www.chestnet.org by clicking the Call for Topics link when it becomes available. To access the page, you will need your ACCP member identification number.

For questions, contact the ACCP at (800) 343-2227 or (847) 498-1400.

TOPIC SUBMISSION DEADLINE:
NOVEMBER 27, 2006
1:00 PM (EASTERN TIME)

ACCP “LEARN” Scholarship Researching the Educational Impact of Medical Education

The ACCP Continuing Education Committee has launched a groundbreaking scholarship program to award and promote research efforts in continuing medical education (CME) to better understand how education designs impact physicians and clinical outcomes.

Up to $15,000 will be awarded to support one 2-year study that:
• Impacts the future development of clinically relevant medical education initiatives within the ACCP.
• Identifies, advances, and promotes the best delivery of medical education.

Applicants must:
• Be an ACCP member.
• Submit proposals to study learning outcomes of ACCP educational activities and measure the effect on physician knowledge and health-care delivery.
• Complete an online application for this award by January 10, 2007.

Learn more and apply at www.chestnet.org/education/scholarship.
Long-Acting Beta-Agonists: True Concern or False Alarm?

BY DR. ALAN FEIN, FCCP; DR. JILL OHAR, FCCP; AND DR. FRANK LEONE, FCCP

Recently a “black box” warning was issued by the FDA for salmeterol and the combination salmeterol/fluticasone (Advair). This warning has been extensively covered in the lay press and has resulted in apprehension and uncertainty about the appropriate role of these agents and about the safety of long-acting beta-agonists (LABA), in general.

This labeling change was based on the results of the SMART study (salmeterol multicenter asthma research trial), a 28-week observational safety study conducted to evaluate the impact of salmeterol on respiratory deaths. Diagnosis of asthma was based on the clinical judgment of the study physician, with exclusion of those with previous use of a long-acting β-agonist. Subjects were randomly assigned to receive either 42 µg of salmeterol to these asthma deaths. There were 13 deaths in the salmeterol group and 3 in the placebo group; 7 of the 13 were African-American, although they represented only 20% of the study population. African-Americans had lower inhaled steroid use (38% vs 49%) and greater utilization of hospital and critical care services. This study remains controversial and the subject of extensive review and opinion. Although concern about increased mortality related to LABA has periodically surfaced over the past 20 years, no specific cause and effect mechanism has been identified to link salmeterol to these asthma deaths.

Another recent development has been the long-awaited preliminary report of the TORCH (TOwards a Revolution in COPD Health) study. TORCH compares the effect of salmeterol/fluticasone 50/500 µg, fluticasone 500 µg, or salmeterol 50 µg vs placebo, when given for 3 years. All-cause mortality was chosen as the primary end point, while COPD morbidity, exacerbations, need for long-term oxygen, and safety were also secondarily examined. Over 6,100 subjects were enrolled. Results reported so far include a 2.6% absolute (17.5% relative) reduction in mortality (p<0.05), a 25% reduction in moderate to severe exacerbations (p=0.001), an improved quality of life by St. George Respiratory Questionnaire, and a 92 ml improvement in FEV1 (p=0.001) in the group receiving the LABA/ICS combination compared with placebo. There were no excess deaths experienced in the salmeterol group, with cardiorespiratory deaths most common (62%), followed by malignancy (21%). Full results await publication; no information regarding the likelihood of type II error is currently available.

The overall safety of these medications in the TORCH study may provide some additional comfort to physicians and patients when using these medications. The reduction in all-cause mortality with combination salmeterol/fluticasone among patients with COPD is also encouraging. We anxiously await the full reporting of these results in order to estimate their clinical impact on the approach to patients with COPD.

References

Disclosures
Alan Fein, MD, FCCP
Consultant fee, speaker bureau, advisory committee, etc: BI and Pfizer and Encyse pharmaceutical
Speaker revenue: Encyse and Baxter
Jill Ohar, MD, FCCP
Product/Research Disclosure Information
Grant monies (from sources other than industry): The Mesothelioma Applied Research Foundation Shareholder: Sepracor Employee: Family member is a Boehringer Ingelheim Representative Consultant fee, speaker bureau, advisory committee, etc: GlaxoStriblEis, Boehringer Ingelheim, Aventis, AstraZeneca
Frank Leone, MD, FCCP
Consultant Arrangements: Pfizer Pharmaceuticals, Inc. (Verenacine Advisory Panel)
Product/Research Disclosure Information
American Lung Association Asthma Clinical Research Centers American Lung Association; Continuum of Tobacco Treatment Training Project Pennsylvania Department of Health: Tobacco Treatment Provider Training Project Montgomery County Health Department: Smoking Cessation for Cancer Patients National Cancer Institute; The PA consortium on tobacco disparities (PACTD)
Pennsylvania Department of Health: Philadelphia Residents Empowered to Stop Smoking (The PRESS project).
Philadelphia Department of Public Health Speakers’ Bureau:Pfizer Pharmaceuticals, inc.; Merck, inc.

Asthma Practice Improvement

The American Board of Internal Medicine has developed the Asthma Practice Improvement Module for use by physicians recertifying in internal medicine and its subspecialties. This self-evaluation tool will focus on physicians’ actual practice patterns on the chronic illness, asthma. The module uses CD-ROM technology to provide a template for chart review of key patient care outcomes and processes, along with a review of key components of the practice system (information management, patient self-care support, access to the practice, patient safety measures, teamwork, and the practice’s improvement process). The module also includes an anonymous telephone survey for patients that addresses functional status, self-care knowledge and behaviors, and satisfaction with care. ABIM aggregates these data to provide an interactive practice work-up report that enables the physician to develop an individualized practice improvement plan based on important and feasible goals for his/her own practice.

Information on the module can be found at www.abim.org. The ACCP offers supplemental educational resources to assist physicians using this module. These can be found at: www.chestnet.org/education/online/abim/chart/index.php and www.chestnet.org/education/online/abim/practice/index.php

November Is COPD Awareness Month

Commemorate COPD Awareness Month and celebrate World COPD Day by supporting programs in your community. Use tools and resources available from the ACCP.

World COPD Day is November 15

Tools and resources related to COPD are available for download or purchase. Learn more at www.chestnet.org/copd.

NEWS FROM THE COLLEGE

Chest Physician • October 2006

Pages 14a—14b
T
here is an often-used anecdote that illustrates the principles of marketing and applies descriptive of the role of the ACCP in the marketplace. If the circus is to come to town and you are a painted sign saying “Circus Coming to the Fairground Sat-

day,” that’s advertising. If you put the sign on the back of an elephant and walk it into town, that’s promotion. If the ele-
phant walks through the streets, that’s publicity. If you get the mayor to laugh about it, that’s public relations.

And, if you planned the whole thing, that’s marketing.

Prior to the creation of the ACCP Mar-
keting Division, departments within the
ACCP were responsible for their own mar-
keting. As the ACCP evolved and grew to
meet the needs of its members, the demand for marketing services in-
creased, and it became clear a formal marketing group was needed. Since its inception in the early 1990s, the ACCP Marketing Division has been planning and executing marketing plans that include advertising, pro-
motion, publicity, and public relations for ACCP products and services.

An ACCP Marketing Committee was established to create a forum for exchange of information and ideas. Comprising ACCP members and staff, the committee first met during CHEST 1999 and set forth priorities and goals. Over time, since that time, it has provided qua-

lified input to help identify member needs and increase the profile of the ACCP. Today, the Marketing Division develops strategic marketing cam-
paigns for the annual CHEST meet-
ing, education courses, and products, ACCP membership, CHEST, the CHEST Foundation, and more.

The science published in CHEST and presented at annual CHEST meetings was increasingly newswor-
thy and recognized by the media. The


ACCP Marketing: Walking Elephants, Laughing Mayors

62.5 mg and 125 mg film-coated tablets

Site of TRACLEER® requires attention to two significant concerns: 1) potential for serious liver injury, and 2) potential for serious cardiovascular disease.

WARNING: Potential liver injury. TRACLEER® causes up to 3-6 fold higher levels of standard (SNL) elevation are seen in patients with concurrent use of CYP3A4 substrates, such as rifampin, decreases in aminotransferase levels were seen in bosentan-treated patients as compared to 29% of placebo-treated patients. In 80% of cases, the decrease occurred during the first 6 weeks of bosentan treatment. During the course of treatment the hemoglobin concentration remained small and does not require dosing adjustment. Dosage Adjustment in Geriatric Patients: Clinical studies of TRACLEER® did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. In general, older subjects tend to be more susceptible to the effects of the CYP3A4 inhibitors, and consequently may require a dosage adjustment. No dosage adjustment of TRACLEER® should be made based on age alone.

Discontinuation of Treatment: There is limited experience with abrupt discontinuation of TRACLEER®. No evidence for a rebound increase in pulmonary vascular resistance has been observed. In patients with pulmonary arterial hypertension, treatment should be interrupted, then re-introduced when aminotransferase levels return to pre-treatment values, continue or re-introduce the

Ventricular dysfunction. There is a lack of data to evaluate the long-term safety of bosentan in patients with New York Heart Association class IV CHF. To date no clinical studies of bosentan have been performed in the treatment of CHF with left ventricular dysfunction. Treatment with bosentan may result in significant increases in plasma concentrations of bosentan. In such patients, bosentan is not effective in the treatment of CHF with left ventricular dysfunction.

Dosage Adjustment in Patients with Hepatic Impairment: Due to the small size of the patient population (n = 13) with severe hepatic impairment who did not receive concurrent treatment with cyclosporine A, the effects of bosentan in patients with hepatic impairment are unknown. The safety and effectiveness of bosentan have not been established in patients with hepatic impairment. bosentan is not recommended in patients with severe hepatic impairment (Child Pugh class C). Treatment with bosentan may result in increases in plasma concentrations of bosentan. In such patients, bosentan is not effective in the treatment of CHF with left ventricular dysfunction.

Dosage Adjustment in Patients with Renal Impairment: Due to the small size of the patient population (n = 13) with severe renal impairment who did not receive concurrent treatment with cyclosporine A, the effects of bosentan in patients with renal impairment are unknown. The safety and effectiveness of bosentan have not been established in patients with renal impairment. bosentan is not recommended in patients with severe renal impairment (creatinine clearance of < 30 ml/min).

Dosage Adjustment in Patients with Pulmonary Arterial Hypertension: In the open-label treatment regimen study with bosentan in patients with pulmonary arterial hypertension, and other diseases. Treatment discontinuations due to adverse effects occurred in 15% of patients in the placebo group and in 13% of patients in the bosentan group. The most common adverse effects were hemoglobin concentration decreases, headache, rash, and gastrointestinal upset.

Dosage Adjustment in Patients with Congestive Heart Failure: In the open-label treatment regimen study with bosentan in patients with congestive heart failure, and other diseases. Treatment discontinuations due to adverse effects occurred in 15% of patients in the placebo group and in 13% of patients in the bosentan group. The most common adverse effects were hemoglobin concentration decreases, headache, rash, and gastrointestinal upset.

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Among the nation’s leading killers, COPD is the only disease with a mortality rate that continues to climb. But, the vast majority of those at greatest risk for the disease are largely unaware of COPD and, in many cases, don’t even realize that their condition has a name.

The National Heart, Lung, and Blood Institute (NHLBI) of the US Department of Health and Human Services recently initiated a national awareness and education campaign to increase recognition and understanding of COPD and its risk factors, and to underscore the benefits of detection and treatment in slowing the disease and improving quality of life. The ACCP has joined NHLBI as a partner in this effort.

This first phase of the NHLBI campaign, COPD: Learn More Breathe Better, will encourage health-care providers, particularly those in the primary care setting, to consider a COPD diagnosis in patients with shortness of breath, excess sputum production, and other symptoms, and to be mindful that proactive treatment may slow the disease progress and improve their patients’ quality of life.

The campaign’s second phase—introducing COPD to men and women at risk—will begin in early 2007. "COPD has always been a top priority for the ACCP. We are excited to join NHLBI in helping to promote better understanding of this disorder among our members, to our colleagues in the primary care arena, and among our patients," said ACCP President, Dr. W. Michael Alberts, FCCP.

ACCP members can access campaign materials, including a pocket reference card; an informational poster for doctor’s offices, clinics, and hospitals; fact sheets for diagnosed patients and those at-risk for COPD; and a speaker’s guide with slide presentations for promoting awareness of COPD to potential patients, as well as among provider peers and colleagues, by visiting the campaign’s Web site at www.LearnAboutCOPD.org.
The milestone is just the latest in a series of developments in the size and stature of the field of palliative care. Between 2000 and 2004, the number of hospital-owned palliative care programs in the United States increased by nearly 75%, jumping from 632 in 2000 to 1,102 in 2004. As of 2004, 63% of large hospitals—those with at least 200 general adult beds—reported that they had some type of palliative care program in operation, according to the Center to Advance Palliative Care.

This summer, palliative medicine received a nod from the Accreditation Council for Graduate Medical Education (ACGME) when the organization voted to approve an accreditation process for hospice and palliative medicine fellowship training programs. ACGME is expected to begin accepting applications in summer 2007.

“We’re well beyond the tipping point,” said Dr. Diane Meier, director of the Center to Advance Palliative Care and director of the Hertzberg Palliative Care Institute at Mount Sinai School of Medicine in New York.

At her institution, palliative care has become so well accepted that asking for a palliative care consult is as routine as calling for an infectious disease consult. Now the focus has shifted from selling the concept of palliative medicine to ensuring that programs around the country have consistently high standards, Dr. Meier said.

Work is already underway in this area. The National Consensus Project for Quality Palliative Care, which is sponsored by three national palliative medicine organizations, has released quality guidelines.

In an effort to ensure that new programs have high-quality processes in place, the Center to Advance Palliative Care launched the Palliative Care Leadership Centers—six centers of excellence in palliative care around the country that train teams of health care providers. The program includes intensive, 2-day training sessions in which teams are sent to one of the six centers and leaders at the centers act as mentors for a year after training.

When the site visits started in 2004, Dr. Meier and others at the Center to Advance Palliative Care estimated that about 30% of the teams trained would successfully establish a program, she said, but it’s been closer to 70% to date.

ProYIhP 2999

## Palliative Care Gains ABMS Subspecialty Recognition

BY MARY ELLEN SCHNEIDER

BYELLEN SCHNEIDER

Elsevier Global Medical News

The field of palliative care took a major step forward in September when members of the American Board of Medical Specialties voted to approve hospice and palliative medicine as a recognized subspecialty.

The application to recognize the subspecialty had broad support and was cosponsored by 10 medical specialty boards. As a result, physicians in a number of specialties—including internal medicine, family medicine, pediatrics, psychiatry, neurology, surgery, emergency medicine, and obstetrics and gynecology—will be able to seek certification.

The first certification examination is expected to be administered in 2008, according to Dr. F. Daniel Duffy, senior advisor to the president of the American Board of Internal Medicine.

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short of making specific treatment recom-
mendations, and instead states that treat-
ment should be individualized, it does
describe patient evaluation.
It is reasonable that patients and their
bed partners be questioned about symp-
toms of sleep-disordered breathing and
that appropriate patients be referred to a
sleep specialist for further evaluation, the
guideline states.
This is particularly important if the pa-
tient has drug-resistant hypertension or
certain risk factors for stroke, such as
ab-
donial obesity and hypertension (Stroke
In making its recommendation, the
American Heart Association/American
Stroke Association Stroke Council cited
data from several studies, including a
case-control study of 181 patients, which
showed an association between excessive
daytime sleepiness (likely caused by ob-
structive sleep apnea) and stroke (odds
ratio 3.07).
The council also cited a 10-year obser-
vational study of more than 1,600 men,
which showed that those patients who had
severe obstructive sleep apnea-hy-
opnea had an increased risk of fatal
and nonfatal cardiovascular events
including stroke, compared with healthy
individuals (odds ratio 2.87 and 3.17,
respectively).
The guideline noted that there are a
number of biologically plausible mecha-
nisms for a link between sleep apnea and
stroke. Dr. Mohsenin agreed.
Several studies suggest that the
mechanism by which sleep-disor-
dered breathing in-
creases stroke risk is by “leading to or
worsening hyper-
tension and heart
disease and possi-
bly by causing
reductions in cerebral blood flow, al-
terred cerebral autoregulation, impaired
endothelial function, accelerated athero-
genesis, hypercoagulability, inflamma-
tion, and paradoxical embolism in
patients with patent foramen ovale,” the
guideline states.
But the real question, Dr. Mohsenin
said, is whether there is an independent
association between sleep apnea and
stroke. A recent study on which he was an
author shows that there is indeed such an
association.
In the observational cohort study of
697 patients with obstructive sleep apnea
and 125 controls (mean apnea-hypopnea
index of 35 vs. 2 in the patients and con-
trols, respectively), obstructive sleep
apnea was found to have a statistically
significant association with stroke or
death (hazard ratio of 1.91) after adjust-
ment for numerous factors, including
age, sex, race, smoking status, al-
cohol consumption, body mass
index, diabetes, hyper-
perlipidemia, atrial fibrillation, and hy-
pertension.
A trend analysis also showed a
significant dose-
response relationship between sleep ap-
nea severity at baseline and development
of stroke or
death from any cause (N En
While randomized controlled trials are
needed to firmly establish a causal link
between sleep apnea and stroke—to “put
the last nail in the coffin and say,
‘OK, sleep apnea is indeed a cause of
stroke in a high-risk patient population,’”
as Dr. Mohsenin put it, the findings in-
creasingly suggest this is the case.
Also, sleep apnea occurs as commonly
in transient ischemic attack as it does in
stroke, further underscoring the need for
sleep apnea treatment in affected patients,
he noted.
In addition, a number of studies have
shown that sleep apnea is associated with
worse functional outcomes in stroke pa-
tients, he said.
Patients with stroke who have sleep
apnea have been shown to have more
delirium, depression, impaired function-
al capacity, longer rehabilitation time,
and longer hospitalization, Dr. Moh-
senin explained.
“Sleep apnea does affect the outcome
of stroke,” he said, and he noted that in
some studies the impact lasted up to
12 months.
Patients who have had a stroke should
be evaluated for sleep-disordered breath-
ing, Dr. Mohsenin advised.
In addition, patients using long-term
CPAP should be reevaluated for residual
symptoms of the disorder to ensure ade-
quate treatment and compliance, he
added.

**Randomized Controlled Trials are Needed to Firmly Establish a Causal Link Between Sleep Apnea and Stroke.**

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**CPAP May Benefit Women at Risk for Preeclampsia**

**By Sharon Worcester**

_Elsevier Global Medical News_

**Salt Lake City —** The use of con-
tinuous positive airway pressure may help
prevent preeclampsia in pregnant women
at risk for the condition, the results of a
small study suggest.
In 9 of 12 women with risk factors
for preeclampsia who used continuous posi-
tive airway pressure (CPAP) and medical
therapy beginning before 9 weeks’ gesta-
tion, blood pressure remained stable and
pregnancy was nor-
mal, Dr. Christian
Guilleminault re-
ported in a poster at
the annual meeting
of the Associated
Professional Sleep
Societies.
Sleep-disordered
breathing has been
suggested by several
studies as a possible contributor to
preeclampsia.
In one study, snoring was linked
with preeclampsia, with the disorder occurring
in 10% of snorers compared with 4% of
non-snorers. In another study, snoring was
shown to be a significant predictor of hy-
pertension and fetal growth retardation,
even after controlling for maternal weight,
age, and smoking status.
Based on such findings, some researchers
have recommended polysomnography and/or
CPAP use in pregnant women with
risk factors—including snoring—for
preeclampsia.
In the current study, all 12 participants
had risk factors for preeclampsia: All were
snorers; seven had hypertension; two had
prior preeclampsia; and three were obese,
with a body mass index greater than
30 kg/m².
The women, who had a mean age of 29
years, underwent polysomnography at a
mean of 7.5 weeks’ gestation, and all had
flow limitations at the nasal cannula with-
out apnea or hypopnea.
Nasal CPAP was used in all participants
at an initial pressure of 5-6 cm H2O, and
in eight women the pressure was increased
to 6.9 cm H2O at between 5 and 6 months’
gestation. Of the seven women with hyper-
pertension at baseline, diastolic blood
pressure below 90 mm
Hg was maintained
without a change in
medication.
All seven of the women delivered healthy,
full-term in-
fants, as did one of
the women with a
history of preeclampsia, reported Dr.
Guilleminault, of the department of psy-
chiatry at Stanford (Calif.) University.
One of the obese women miscarried at
near 14 weeks’ gestation, and another de-
livered at 34 weeks but did not develop
preeclampsia.
The third obese patient and the second
woman with prior preeclampsia devel-
oped clinical features of preeclampsia, and
both underwent cesarean section at 7.5
months’ gestation.
Treatment with nasal CPAP with initia-
tion prior to 9 weeks’ gestation was associ-
ated in this study with stable blood pressure
and normal pregnancy in most women
with risk factors for preeclampsia, Dr.
Guilleminault concluded.
New Risk Factors Found for Postoperative VTE

Philadelphia — Pneumonia was one of five new risk factors for postoperative venous thromboembolism identified in an analysis of more than 75,000 patients.

Other new risk factors for venous thromboembolism (VTE) were the need for a blood transfusion because of bleeding, renal insufficiency, urinary tract infection, and a low serum albumin level, Dr. Chethan Gangireddy said at the Vascular Annual Meeting.

“These newly described risk factors can aid in further stratifying a patient’s risk for postoperative VTE,” said Dr. Gangireddy.

Independent Risk Factors For VTE After Surgery

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>Cardiac arrest</td>
</tr>
<tr>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Blood transfusion because of bleeding</td>
</tr>
<tr>
<td>Renal insufficiency</td>
</tr>
<tr>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>Hemodialysis for renal failure (protective)</td>
</tr>
<tr>
<td>Diabetes (protective)</td>
</tr>
<tr>
<td>High level of serum albumin (protective)</td>
</tr>
</tbody>
</table>

Note: Based on data from 75,711 patients. Source: Dr. Gangireddy

The overall incidence of VTE was 0.7%, but the incidence varied significantly based on the type of surgery. In a multivariate analysis that evaluated the independent risk added by many different clinical and demographic factors, pneumonia was the strongest risk factor, boosting the risk of venous thromboembolism 2.7-fold.

Several other risk factors each boosted the risk for VTE by about twofold (see table), and three factors were found to reduce the VTE risk. In an analysis of the two most common manifestations of VTE, the list of significant risk factors for causing deep vein thrombosis was found to be different from the list linked with pulmonary embolism.

The top risks for deep vein thrombosis were need for a transfusion due to bleeding (a 3.3-fold increased risk), pneumonia (a 2.5-fold increased risk), and urinary tract infection (a 1.7-fold increased risk).

For pulmonary embolism, the top risk factor was demonstrated to be cardiac arrest (7.6-fold increased risk), followed by pneumonia (3.8-fold increased risk) and need for a transfusion (2.4-fold increased risk).

Another finding of the study was that patients with venous thromboembolism had a 2.4-fold increased risk of death compared with all other patients, Dr. Gangireddy said.

### Table 3: Summary of Advise Events

<table>
<thead>
<tr>
<th>Zemaira</th>
<th>Prostacyclin</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects treated</td>
<td>859</td>
</tr>
<tr>
<td>No. of subjects with adverse events regardless of causality (%):</td>
<td>69 (78%)</td>
</tr>
<tr>
<td>No. of subjects with related adverse events (%)</td>
<td>16 (19%)</td>
</tr>
<tr>
<td>No. of subjects with unrelated adverse events (%)</td>
<td>0</td>
</tr>
<tr>
<td>No. of infusions</td>
<td>1192</td>
</tr>
<tr>
<td>No. of adverse events regardless of causality (per person infused):</td>
<td>298 (2.0%)</td>
</tr>
<tr>
<td>No. of related adverse events (per person infused):</td>
<td>60 (0.0%)</td>
</tr>
</tbody>
</table>

The frequencies of adverse events per infusion that were 20-40% in Zemaira-treated subjects, included: bacteremia (1.6%), staphylococcal (0.9%), coagulase-negative (0.8%), staphylococcal (0.3%), coagulase-negative (0.2%), and Pseudomonas (0.2%).

Adverse events were considered related if the event occurred at a rate of 0.2% or more per infusion: abdominal pain, diarrhea, dizziness, erythema, myalgia, pruritus, tachycardia, cough, chest pain, dyspnea, hematuria, injection-site reaction, laryngitis, nausea, and pancreatitis.

Difference: statistical large dose was noted on a routine data set of one subject at 124. Calcium content could not be determined.

In a retrospective analysis, during the 10-24 follow-up period of the 23-episode clinical study, 6 subjects (20% of the 30 treated with Zemaira) had a total of 7 exacerbations of their chronic obstructive pulmonary disease (COPD). - three subjects (6%) of the 14 treated with Prostacyclin had a total of 11 exacerbations of this COPD. The observed difference between groups was 49% (95% confidence interval from 3% to 76%).

### HOW SUPPLIED

Zemaira is supplied in a lyophilized form containing the labeled amount of functionally active PGI 2 as stated on the label. Each product package (NDC: 0553-3001-01) contains one single-use vial of Zemaira one 20 mg of Stelara for Injection, IPS (bevacizumab), and one vial busercept powder.

### STORAGE

When stored at 25° to 30°C (77°F), Zemaiz is stable for the period indicated by the expiration date on the label. Avoid freezing which may damage containers for the patient.

### PROSTACYCLIN

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**Adapted from:** 1933-04 Revised: March 2006

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