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ELSEVIER GLOBAL MEDICAL NEWS

After children stopped daily asthma therapy, they began to have the same outcomes as placebo-treated patients by adolescence.

Benefits Fade When Asthma Therapy Stops

BY JEFF EVANS
Elsevier Global Medical News

The beneficial effects of long-term treatment with inhaled anti-inflammatory medications in preadolescent children with mild to moderate asthma do not appear to last when the medications are discontinued during adolescence, according to the results of an observational follow-up study of patients in the Childhood Asthma Management Program trial.

Once patients discontinued their required daily therapy, over time they began to have the same outcomes as placebo-treated patients in terms of asthma control and pulmonary function, Dr. Robert C. Strunk of Washington University, St. Louis, and his colleagues reported in the Journal of Pediatrics (2009 Jan. 23 [doi:10.1016/j.jpeds.2008.11.036]).

In the original Childhood Asthma Management Program (CAMP) randomized trial, 4.3 years of treatment with budesonide 200 mcg twice daily led to significantly fewer hospitalizations, urgent care visits, courses of prednisone, and days in which other asthma medications were needed than did treatment with placebo. Treatment with nedocromil 8 mg twice daily for the same length of time in other patients also led to significantly fewer prednisone courses and urgent hospital visits than did placebo.

Of 1,041 children in the original CAMP cohort, 941 enrolled in a posttrial follow-up study for a mean duration of 4.8 years. In that follow-up period, Dr. Strunk and his colleagues allowed patients to continue using any open-label asthma medications that they had used in addition to the study medication during the trial. The investigators also prescribed open-label asthma medications, based on National Asthma Education and Prevention Program guidelines, to any patients whose asthma was too severe to switch to albuterol alone during an 8-month washout period between the trial and follow-up period.

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Tight Glucose Control Raised Mortality in ICU

But some caution against 'overreaction.'

BY MARY ANN MOON
Elsevier Global Medical News

Tight glucose control among ICU patients significantly raised the risk of death within 90 days, compared with conventional glucose control, Dr. Simon Finfer reported at the International Symposium on Intensive Care and Emergency Medicine in Brussels.

In a large international, randomized clinical trial, a blood glucose target of less than 180 mg/dL resulted in lower mortality than a target of 81-108 mg/dL. "On the basis of these results, we do not recommend use of the lower target in critically ill adults," Dr. Finfer said.

Hyperglycemia is common in acutely ill patients. Intensive glucose control for ICU patients has been recommended by many professional organizations "on the assumption that treatment aimed at normoglycemia will benefit patients," said Dr. Finfer of the George Institute for International Health, Sydney.

However, some clinicians are reluctant to attempt tight glucose control because the risks—primarily the higher incidence of severe hypoglycemia—may outweigh the benefits.

Several studies have yielded conflicting results. Dr. Finfer and his associates undertook the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial to determine whether tight glucose control reduces mortality at 90 days.

The study involved 6,104 medical and surgical patients admitted to ICUs in 38 academic tertiary care hospitals and 4 community hospitals in Australia, New Zealand, and North America. Of the 6,030

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INSIDE

Insurance May Not Mean Asthma Control

BY DENISE NAPOLI
Elsevier Global Medical News

WASHINGTON — Health insurance coverage and access to a health care provider did not translate into better asthma control in a study of Denver-area schoolchildren.

The findings, reported in a poster presentation at the annual meeting of the American Academy of Allergy, Asthma & Immunology, seem to disprove the commonly held notion that having health coverage is the most important step toward successful asthma management.

Dr. Tracy Kruzick and her colleagues from National Jewish Health in Denver surveyed 728 families of local students with asthma about medical coverage and their child's asthma symptoms; 153 completed the questionnaire and were enrolled in the Denver Public School Asthma Program. The mean age of the students was 9 years.

Although 78% of the families qualified for reduced lunch, 89% reported having medical

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Glucose Control Debated

ICU • *from page 1*

subjects for whom study data were available, 3,014 were randomized to receive conventional glucose control (with a target of 180 mg/dL or less), and 3,016 to receive tight glucose control (with a target of 81-108 mg/dL) with intravenous infusions insulin infusions. The mean duration of study treatment was 4 days.

Ninety-day mortality was 24.9% with conventional glucose control and 27.5% with tight glucose control, a significant difference. "This represents a number needed to harm of 38," Dr. Finfer said (N. Engl. J. Med. 2009;360:1283-97). Median survival time was shorter in the tight-control than in the conventional-control group.

Tight glucose control did not improve mortality in certain subgroups of patients who might be expected to benefit from more stringent control. Mortality was similar between surgical patients and medical patients, between patients with or without diabetes, between those with or without severe sepsis, and between those with high or low Acute Physiology and Chronic Health Evaluation (APACHE) scores.

Severe hypoglycemia, defined as a blood glucose level of 40 mg/dL or less, occurred in 206 (6.8%) of the tight-control group, compared with 15 (0.5%) of the conventional-control group. There were 272 episodes of severe hypoglycemia among patients under tight glucose control, compared with 16 episodes among those under conventional glucose control.

There were no significant differences between the two groups in ICU or hospital lengths of stay, the number of single or multiple organ failures that developed, the number of days on mechanical ventilation or on renal replacement therapy, or the rates of positive blood cultures and red-cell transfusions.

"Our findings suggest that a goal of normoglycemia for glucose control does not necessarily benefit critically ill patients and may be harmful," Dr. Finfer said. "Whether the harm we observed resulted from the reduced blood glucose level, increased administration of insulin, occurrence of hypoglycemia, methodologic factors specific to our trial, or other factors is unclear."

According to a joint statement released by the American Diabetes Association and the American Association of Clinical Endocrinologists, this study "should *not* lead to an abandonment of the concept of good glucose management in the hospital setting," and should not "swing the pendulum of glucose control too far in the other direction," leading to complacency about uncontrolled hyperglycemia. "Until more information is available, it seems reasonable for clinicians to treat critical care patients with the less intensive—yet good—glucose control strategies used in the conventional arm of the NICE-SUGAR trial."

Clinicians "are now left in something of a quandary," because many hospitals have already adopted "the automatic and seamless use of insulin infusion in patients in the ICU," Dr. Silvio E. Inzucchi and Dr. Mark D. Siegel of Yale University, New Haven, Conn., wrote in an editorial (N. Engl. J. Med. 2009;360:1346-8). "We would caution against any overreaction to the NICE-SUGAR findings," they said.

"It would be a disservice to our critically ill patients to infer from the NICE-SUGAR data that neglectful glycemic control involving haphazard therapeutic approaches (e.g., use of insulin 'sliding scales')—all too common a decade ago—is again acceptable practice in our ICUs," Dr. Inzucchi and Dr. Siegel said.

Dr. Finfer reported receiving reimbursement for travel to present research results at scientific meetings from Eli Lilly & Co., Cardinal Health Inc., and CSL Bioplasma Ltd., as well as reimbursement for serving on steering committees for studies sponsored by Eli Lilly and Eisai Inc. Dr. Inzucchi reported receiving research funding from Eli Lilly. ■

Outcomes Gap Narrowed

Benefits • *from page 1*

In the three groups, the patients did not use medication for asthma for 42%-45% of their time during follow-up. Patients who had received budesonide required 29% fewer prednisone courses and 36% fewer urgent care visits than did patients who had received placebo. There were no differences in those measures between patients who had received nedocromil and those who had received placebo.

However, the significant reductions in prednisone courses and urgent care visits that occurred after discontinuation of budesonide "must be considered in the context of the very low rates of these events in all groups during the posttrial follow-up period … [and] likely are not clinically relevant," the investigators wrote.

Based on the results, the number of patients who would have had to have been treated with budesonide for 4.3 years to prevent one course of prednisone per year was much lower during treatment in the CAMP trial than during the follow-up period (2 vs. 15). The number of patients who would have had to have been treated with budesonide for 4.3 years to prevent one urgent care visit per year was similarly skewed in favor of the active treatment period rather than the period after discontinuation of medication (10 vs. 32).

The number of prednisone courses and urgent care visits steadily declined for all patients, regardless of treatment, as they were followed from a mean age of 8.9 years at the time of randomization to a mean age of 18.1 years at the end of the posttrial follow-up period.

"These reductions are consistent with the known improvement in the clinical course of asthma that occurs as children reach adolescence. The reductions also could be related in part to a reluctance of the treating physicians to prescribe prednisone during acute exacerbations compared with the protocol-mandated use of prednisone for exacerbations during the trial," wrote Dr. Strunk and his coinvestigators, none of whom reported any conflicts of interest.

The investigators saw no differences in spirometry measurements (percent of predicted forced expiratory volume in 1 second and percent of predicted forced vital capacity both before and after bronchodilator use) between the groups during the posttrial follow-up period.

None of the groups showed differences in bronchodilator reversibility or methacholine responsiveness.

At the end of the CAMP trial, budesonide-treated patients had significantly decreased height in comparison to placebo-treated patients (1.1 cm) that was maintained through the end of the posttrial follow-up period (0.9 cm). The decreased height in girls (1.7 cm) was statistically significant, but the decreased height in boys (0.3 cm) was not. However, 25% of the girls and 54% of the boys had not yet achieved adult height by that time. ■

Dr. Philip Marcus, MPH, FCCP, comments: *This is yet another reminder that asthma must be considered a chronic illness that requires continuous long-term therapy for management. Just like many other chronic illnesses that plague society, such as hypertension and diabetes mellitus, the illness does not resolve with suppressive therapy. However, patients' outcomes are better with long-term therapy, and the use of appropriate long-term medications is indeed appropriate for the long haul.*

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U.S. Smoking Rate Drops to All-Time Low

BY MITCHEL L. ZOLER
Elsevier Global Medical News

The prevalence of U.S. cigarette smokers hit a historic low in 2007, falling to just under 20% of the adult population, according to data released in mid-March by the Centers for Disease Control and Prevention.

Physicians on the front line against tobacco use hailed this as a milestone in the ongoing effort to cut smoking by Americans. They also see the rise in the federal tobacco excise tax on April 1 that boosts the tax on a pack of cigarettes from $0.39 to $1.01 as an important escalation in the fight against tobacco that will likely lower smoking rates further.

Cutting the smoking prevalence rate among adults across the United States "is an extraordinary accomplishment," said Dr. Michael C. Fiore, professor of medicine at the University of Wisconsin School of Medicine and Public Health in Madison and director of the Center for Tobacco Research and Intervention. In the mid-1960s, about 43% of all American adults smoked, so cutting the rate by more than half, to a median of 19.8% in 2007, "is one of the seminal public health achievements in our time," he said. "If you look at the past 50 years there has been a remarkably straight line of decline of about 0.5% per year."

Even over the decade that is covered by the new CDC report, smoking rates showed a meaningful decline from a median rate of 22.9% in 1998 to the 19.8% rate in 2007 (MMWR 2009;58:221-6).

"Every downward reduction is a positive achievement," said Dr. Alan Blum, professor of family medicine at the University of Alabama, Tuscaloosa, and director of the Center for the Study of Tobacco and Society.

But physicians interviewed cautioned that the rate must be lowered even more. "We cannot be complacent," Dr. Blum said. "Physicians need to be on the front lines working with every patient who smokes and their family."

The new CDC statistics also highlighted the shortcomings of efforts against smoking. In 2000, the U.S. Department of Health and Human Services set U.S. health goals for the upcoming decade in Healthy People 2010. One of the goals was to have a national smoking prevalence rate of 12%. The 2007 rate of 19.8% shows that the goal will not be met.

"The Healthy People 2010 goal was ambitious, and rightly so. The progress [on smoking rates] is encouraging, but slower that it should be. The fact that some states are approaching [the Healthy People 2010 goal] shows that the target was reasonable," said Dr. Steven A. Schroeder, professor of health and health care at the University of California, San Francisco, and director of the UCSF Smoking Cessation Leadership Center.

In 2007, the only states or territories at or close to the 2010 goal were Utah (11.7%), Puerto Rico (12.2%), and the U.S. Virgin Islands (8.7%). But California, with a 2007 rate of 14.3% compared with a 1998 rate of 19.2%, showed a trend that may bring it close to the goal when the 2010 numbers are tallied.

The April rise in the federal excise tax is likely to support the downward momentum. Cigarette smoking is very price-sensitive despite being addictive, Dr. Fiore noted. The added $0.62 in tax per pack may lead to quitting by more than 1.15 million adult smokers and may prevent about 1.45 million youths from starting to smoke, according to an estimate calculated by Frank J. Chaloupka, Ph.D., professor of economics at the University of Illinois at Chicago.

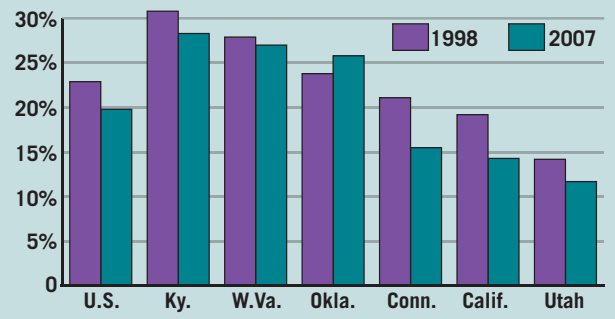
In addition to cost, four other factors have also helped drive smoking rates down, Dr. Fiore said:

- The increase in smoke-free ordinances that has led to a "de-normalization" of smoking;
- The increased recognition of the adverse health effects of smoking, including the danger from second-hand smoke;
- State-sponsored initiatives against smoking, although as the CDC report noted funding for these programs was cut by 28% during 2002-2005 (and yet smoking rates fell during this period despite reduced spending by states on tobacco prevention and cessation programs); and
- Development over the past 12 years of an evidence base for which medical treatments are effective in helping people quit.

The CDC report also documented the remarkable regional variation in U.S. smoking rates, from the lowest state rates in 2007 of 11.7% in Utah and 14.3% in California to the highest rates of 28.3% in Kentucky and 27.0% in West Virginia. (See graph.)

"Smoking is concentrated among those who are poor and have less education," Dr. Schroeder said. States with high smoking rates also generally have low tobacco taxes and have failed to pass laws mandating cleaner indoor air. ■

Smoking Prevalence for Selected States



Note: Based on data from the Behavioral Risk Factor Surveillance System.

Source: MMWR

Ozone Pollution Increased Risk Of Respiratory Mortality

BY MARY ANN MOON
Elsevier Global Medical News

Ozone exposure significantly increased the risk of death from respiratory causes by 2%-3%, according to a report in the March 12 issue of the New England Journal of Medicine.

"Although this increase may appear moderate, the risk of dying from a respiratory cause is more than three times as great in the metropolitan areas with the highest ozone concentrations as in those with the lowest ozone concentrations," said Michael Jerrett, Ph.D., of the University of California School of Public Health, Berkeley, and his associates.

The investigators used data from an American Cancer Society cohort study to examine whether ozone exposure raises all-cause, respiratory, and/or cardiovascular mortality. Previous studies on this issue were inconclusive because they were short term, did not show a significant effect, or were based on limited data, the researchers noted.

The new study assessed causes of death in 448,850 adults residing in 96 U.S. metropolitan statistical areas where air pollution is monitored. The subjects were assessed beginning in 1982, when they were at least 30 years of age, through 2000.

There were 118,777 deaths during 18 years of follow-up. A total of 48,884 were attributed to cardiovascular causes and 9,891 were attributed to respiratory causes.

Analysis revealed that exposure to ozone pollution alone was significantly correlated with both respiratory and cardiovascular mortality. However, when the data were adjusted to account for exposure to fine particulate matter, only the correlation with respiratory death was significant.

That relationship between ozone exposure and respiratory death remained significant when the analysis was further controlled for age, race, income, smoking status, geographic region, and average ambient temperature, Dr. Jerrett and his colleagues wrote (N. Engl. J. Med. 2009;360:1085-95).

Because the association of ozone with cardiovascular death was affected by adjustment for particulate-matter pollution, it was not possible "to determine precisely the independent contributions of these copollutants to the risk of [cardiovascular] death," they noted.

The study could not account for geographic mobility in the cohort during the extensive follow-up. Census data indicate that each year, approximately 2%-3% of the population moved to a different state.

The study was supported by the Health Effects Institute, Boston, a nonprofit group that supports pollution research. ■

Inadequate Vitamin D Seen In Systemic Sclerosis

BY SHERRY BOSCHERT
Elsevier Global Medical News

SAN FRANCISCO — A study of 156 patients with systemic sclerosis in two European cities found that vitamin D deficiency was common, present in 28%.

Deficient levels of serum 25-hydroxyvitamin D (25[OH]D)—less than 10 ng/mL—were seen in 29 (32%) of 90 patients in Paris and 15 (23%) of 66 in Cagliari in southern Italy, Dr. Alessandra Vacca and her associates reported in a poster presentation at the annual meeting of the American College of Rheumatology. In addition, 84% of all patients had insufficient vitamin D levels (less than 30 ng/mL), seen in 75 (82%) of the Parisians and 57 (86%) of the Italians.

The mean vitamin D value in the two cohorts was 19 ng/mL, said Dr. Vacca of the University of Cagliari. The rates of vitamin D deficiency did not differ significantly between cities and so were independent of the different UV radiation levels in the northern and southern cities. Rates of vitamin D deficiency also were independent of usual levels of vitamin D supplementation (800 IU/day), taken by 30% of Parisian patients and 45% of Italian patients.

Because conventional doses of vitamin D supplementation did not prevent vitamin D deficiency, higher-dose supplementation may be needed in patients with systemic sclerosis, she said.

Low vitamin D levels were associated with pulmonary fibrosis, systolic pulmonary arterial hypertension, and inflammatory activity indicated by acute phase reactants—erythrocyte sedimentation rate and C-reactive protein values. There was a significant negative correlation between low vitamin D levels and European disease activity scores.

Low vitamin D levels may be linked to multiple risk factors, Dr. Vacca suggested, including scarce sun exposure due to disability, insufficient intake and malabsorption of vitamin D, or use of drugs that can alter metabolism of vitamin D, such as steroids.

The investigators reported no relevant conflicts of interest. ■

Environmental Cleaning Reduced MRSA Risk in ICUs

A three-part intervention in intensive care units cut MRSA and VRE environmental contamination.

BY MIRIAM E. TUCKER
Elsevier Global Medical News

A three-part environmental cleaning intervention cut the risk to patients of acquiring methicillin-resistant *Staphylococcus aureus* from a prior infected room occupant by more than half in a retrospective study of 13,370 stays in 10 intensive care units.

The findings, presented by Rupak Datta at the annual meeting of the Society for Healthcare Epidemiology of America (SHEA), follow two previous studies by Mr. Datta and his associates. One showed that admission to an ICU room whose prior occupant was a carrier of either MRSA or vancomycin-resistant enterococci (VRE) raised the chance of MRSA or VRE acquisition by 40%, presumably through environmental contamination (Arch. Intern. Med. 2006;166:1945-51).

Subsequently, the investigators showed that a three-part intervention reduced MRSA and VRE environmental contamination in ICUs. The intervention involved immersion of cleaning cloths in a bucket of cleaning solution (rather than simply spraying or pouring the solution from a bottle), an educational campaign focused on infection transmission and proper cleaning procedures, and feedback regarding the removal of intentionally applied marks visible only under ultraviolet light (Infect. Control Hosp. Epidemiol. 2008;29:593-9).

In the current study, conducted over a 20-month period (September 2003–April 2005) at a large, tertiary care academic medical center, the rate of MRSA and VRE acquisition before the three-part cleaning intervention was implemented, was compared with a 20-month period (September 2006–April 2008) after it was in place. Routine admission and weekly screenings conducted during both periods revealed that during the preintervention period, 3.9% of 1,454 patients whose room had a prior occupant with MRSA acquired the pathogen, compared with 1.5% of the 1,443 in such a room during the intervention.

"This study suggests that additional measures over and above national guidelines can be important in reducing transmission in high-risk patient care areas such as the ICU," Mr. Datta, an MD/PhD candidate at the University of California, Irvine, said during a press briefing held before the SHEA meeting.

The cleaning procedure's impact also was seen among patients admitted to rooms without a MRSA-positive prior occupant (2.9% of 8,697 before the intervention vs. 1.6% of 10,406 during the intervention), but the impact was less strong for the acquisition of VRE regardless of room assignment: Of patients with a VRE-positive prior room occupant, 4.5% of 1,291 acquired VRE with the intervention vs. 3.5% of 1,446 without, as did 2.8% of 9,058 vs. 2.0% of 10,425 of those without a prior infected room occupant.

BEFORE THE INTERVENTION, 3.9% OF PATIENTS WHOSE ROOM HAD A PRIOR OCCUPANT WITH MRSA ACQUIRED THE PATHOGEN, VS. 1.5% DURING THE INTERVENTION.

Odds ratios for MRSA acquisition in patients with a previous MRSA-positive room occupant were significant in the preintervention period (1.4) but not the intervention period (1.1). The risk of acquiring VRE when inhabiting a room with an infected prior occupant was significantly increased before and during the intervention.

For both MRSA and VRE, the absolute risk appeared diminished during the intervention regardless of room assignment, Mr. Datta reported.

Asked to comment on the findings during the press briefing, Dr. Neil Fishman, SHEA president-elect, noted that this study is one of a small number that focus on the environmental aspect of hospital infection control as opposed to handwashing and other hygiene behaviors.

"There's frequently very little training for environmental staff. I believe this highlights the need for better training and for standardization of methods in the way rooms are cleaned. I think this is a very important study that will contribute to the prevention of infections and prevention of transmission of resistant organisms in the health care setting," said Dr. Fishman, director of the department of health care epidemiology and infection control, and director of the antimicrobial management program, for the University of Pennsylvania, Philadelphia.

The research was funded by the Prevention Epicenters Program of the Centers for Disease Control and Prevention and a grant from the National Institutes of Health. ■

Candida Infections Increase Hospital Stay, Mortality

BY MICHELE G. SULLIVAN
Elsevier Global Medical News

NASHVILLE, TENN. — *Candida* infections are bad news for patients who require mechanical ventilation during a stay in the intensive care unit, significantly increasing the hospital length of stay and doubling the risk of death.

The factors influencing these risks remain a chicken-and-egg scenario, however, Dr. Marc M. Perrault concluded in a poster presented at the annual congress of the Society of Critical Care Medicine.

"Whether *Candida* species colonization of the respiratory tract secretions is a marker of disease severity or actually contributes to prolonged mechanical ventilation, ICU and hospital stay, and mortality requires further evaluation," said Dr. Perrault, a pharmacist at the McGill University Health Center in Montreal. "The role of antifungal therapy in these patients also remains to be determined."

Dr. Perrault and his colleagues retrospectively analyzed data collected during a large randomized trial that randomized 740 critically ill, mechanically ventilated patients to either bronchoscopy or endotracheal aspiration, followed by a second randomization to treatment with meropenem alone or in combination with ciprofloxacin.

The analysis examined outcomes in the 274 patients who had negative bacterial cultures on enrollment; 64 of these subsequently tested positive for a *Candida* species. The patients' mean age was 60 years; their mean APACHE II score was 20. At baseline, only three characteristics were significantly different between the groups: antibiotic use in the past 3 days, respiratory rate, and white blood cell count. The final analysis controlled for all three of these factors.

In the univariate analysis, 14-day mortality was not significantly different between the groups. However, at 28 days, patients with *Candida* infections were more than twice as likely to have died—31% vs. 15%, a significant difference. ICU mortality was also significantly higher in the *Candida* group (29% vs. 14%, odds ratio 2.65). Cumulative in-hospital mortality was more than twice as common in *Candida*-infected patients (43% vs. 20%), with a highly significant *P* value of less than .001.

When the researchers controlled for the identified factors, patients with *Candida* infections were still more than twice as likely to die in the hospital as those without the infections.

Intravenous antifungal treatment was given to 15 patients with *Candida* infections (22%) and 26 without (13%). None of the treated patients developed candidemia, but the report did not mention how many untreated patients developed that complication. ■

Pages 4a—4b

Insurance Was No Guarantee

Asthma Control • *from page 1*

insurance, 60% of which was a public plan, said Dr. Kruzick.

Although 92% of parents reported that a physician currently was caring for their child's asthma—in most cases a primary care provider—Dr. Kruzick said she believes primary care physicians aren't finding time in the annual well-child exams for asthma education. "Patients aren't getting the information from their doctors," she said.

Among insured children, 39% of parents reported hospitalization relating to their child's asthma. That percentage climbed significantly to 53% among children without health coverage.

A total of 56% of insured children, compared with 67% of uninsured children, reported receiving emergency care for their asthma. Even more startling was that 58% of students with identified medical providers reported using emergency care, compared with 27% of those without a physician managing their asthma.

Almost a third (32%) of parents reported uncontrolled nighttime asthma in their insured children, compared with 20% in uninsured children, a significant difference. The trend for uncontrolled daytime symptoms was similar but not significant, with 30% of insured children having uncontrolled symptoms, compared with 27% of uninsured children.

The study is likely to be an underestimate of the true prevalence of uncontrolled asthma symptoms in this population, said Dr. Kruzick, because many patients with such symptoms "think they're normal." They may also think that it is "normal" to receive occasional emergency care. "We need to change how families perceive their control," she said.

Dr. Kruzick and her colleagues are working on the results from a second round of questionnaires that were completed after some asthma education programs were run at the school level.

The study also illustrates "the need for programs that can identify and monitor children at risk for high asthma morbidity" in this population, the authors concluded.

Dr. Kruzick reported no conflicts of interest, but three of her coauthors reported relationships with multiple pharmaceutical companies. ■

Pertussis Vaccine Not Linked to Wheezing, Asthma

BY MICHELE G. SULLIVAN
Elsevier Global Medical News

Pertussis vaccination in infancy doesn't appear to increase the risk of wheezing or asthma during childhood and, in fact, may be slightly protective against the disorders, a large population-based study concluded.

The analysis by Ben D. Spycher, a researcher at the University of Bern (Switzerland) and his colleagues, was based on data from Britain's National Health Service and from a large respiratory cohort study. It compared rates of new-onset wheeze and asthma occurring after 4 months of age with pertussis vaccinations in 6,048 children who were followed for up to 10 years (Pediatrics 2009;123:944-50).

After inclusion of their child in the cohort, parents received four follow-up questionnaires regarding the occurrence of respiratory symptoms. These data were linked with vaccination records in the national health database, thus eliminating the problems of bias and parental recall that the authors said have plagued previous studies on the issue.

Rates of new-onset wheeze and diagnosed asthma were calculated for both the overall period and for a shorter period beginning at age 36 months.

There were 2,426 cases of new-onset wheeze in the group. In both time frames, analysis showed that children who were fully vaccinated were slightly, but not significantly, less likely to develop wheezing.

The outcomes were similar for diagnosed asthma, they noted. A sensitivity analysis that replaced pertussis vaccination with exposure to other vaccines administered concurrently yielded similar results, providing at least a suggestion that the other vaccinations (diphtheria, tetanus, polio, and *Haemophilus influenza*e type b) also did not increase the risk of wheezing or asthma, the authors said.

The work was supported by national grants from Switzerland and the United Kingdom. The authors declared no financial conflicts relevant to the study. ■

Dr. Burt Lesnick, FCCP, comments: *Parents and physicians have proposed a causal link between childhood vaccination and increased asthma incidence. This study effectively counters the concept.*

Apnea May Increase Postop Pulmonary Complications

BY DAMIAN McNAMARA
Elsevier Global Medical News

MIAMI BEACH — Obstructive sleep apnea is an emerging risk factor for postoperative pulmonary complications, and although evidence does not yet support universal screening, it may be worthwhile to delay elective surgery and test some patients for apnea, Dr. Gerald W. Smetana said.

"If it's not urgent surgery, take a time-out and test to confirm sleep apnea," he said. "The evidence is more compelling now."

In one study, researchers prospectively assessed 172 patients with at least two risk factors for obstructive sleep apnea before surgery and measured clinical severity using home nocturnal oximetry (Chest 2008;133:1128-34). They found that patients who experienced five or more oxygen desaturations per hour had significantly higher rates of postoperative pulmonary complications than did those with fewer episodes (15% vs. 3%, adjusted odds ratio 7.2).

Postop complications in the study were respiratory (nine patients), cardiovascular (five patients), bleeding (two patients), and gastrointestinal (one patient). Although the numbers were small, results were "pretty significant" for pulmonary complications, Dr. Smetana said at a meeting on perioperative medicine sponsored by the University of Miami.

Advanced age, American Society of Anesthesiologists' class of 2 or greater, functional dependence, chronic obstructive pulmonary disorder (COPD), and heart failure are other risk factors identified in the American College of Physicians guidelines on "risk assessment for and strategies to reduce perioperative pulmonary complications for patients undergoing non–cardiothoracic surgery" (Ann. Intern. Med. 2006;144:575-80).

"There is class A evidence that these are risk factors," said Dr. Smetana, a coauthor of the ACP guidelines and an attending physician in the division of general medicine and primary care at Beth Israel Deaconess Medical Center in Boston. "Pulmonary vary from cardiovascular risks in an important way—procedural risks are more important than patient risk factors. Even relatively healthy patients can have risk of pulmonary complications," he said. Pulmonary complications include pneumonia, respiratory failure, atelectasis, bronchospasm, and exacerbation of COPD.

A meeting attendee asked about asthma. "If it is well controlled, surprisingly, it is not a risk factor for postoperative pulmonary complications," said Dr. Smetana, who is also on the medicine faculty at Harvard Medical School, Boston.

In terms of risk reduction, lung expansion modalities are the only intervention with good evidence, he said.

Active muscle training before surgery reduces pulmonary complications in high-risk patients, according to a randomized trial of 279 elective coronary artery bypass graft patients (JAMA 2006;296:1851-7). Preoperative inspiratory muscle training reduced postoperative high-grade pulmonary complications (OR 0.52) and pneumonia (OR 0.40), compared with a usual-care group.

In a meta-analysis, postoperative continuous positive airway pressure lowered overall pulmonary complications after abdominal surgery (Ann. Surg. 2008;247:617-24), making it "a good option for patients who can't tolerate active muscle training," said Dr. Smetana. ■

Pulmonary Hypertension Linked to Surgical Complications

BY DAMIAN McNAMARA
Elsevier Global Medical News

MIAMI BEACH — Pulmonary hypertension was an independent risk factor for perioperative complications among patients undergoing noncardiac surgery within 2 years of pulmonary artery catheterization, according to the first case-controlled study to assess the issue.

Although considered high risk, pulmonary hypertension currently is not recognized as a perioperative risk factor in that patient population, Dr. Roop K. Kaw said.

Dr. Kaw of the Cleveland Clinic and his colleagues reviewed the records of 5,445 patients who had pulmonary artery catheterization between January 2002 and December 2006. They identified 528 adults who had elective noncardiac surgery from that group, including 96 patients with angiographically proven pulmonary hypertension. They compared perioperative outcomes for those 96 patients with 77 controls who had similar surgeries but who had mean pulmonary artery pressure less than 25 mm Hg.

Mean patient age was 61 years, 56% were men, and the mean body mass index was 30 kg/m^2.

In all, 27 patients developed significant perioperative complications. Of those 27 patients, 25 (93%) were in the pulmonary hypertension group, 1 of whom died, Dr. Kaw said at a meeting on perioperative medicine sponsored by the University of Miami.

"We could not look at mortality—we had only one death—so, morbidity and mortality were combined," said Dr. Kaw.

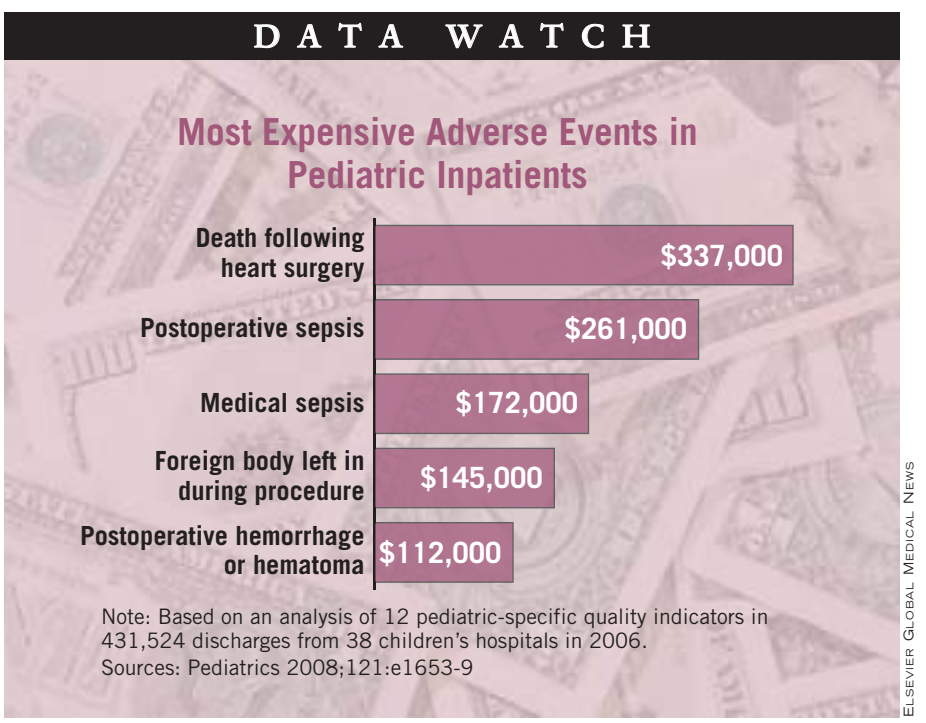
Heart failure, sepsis, hemodynamic instability, and respiratory failure were significantly more likely in the pulmonary hypertension group than in controls, Dr. Kaw said. Patients with pulmonary hypertension also tended to stay in the ICU longer.

Besides mean pulmonary artery pressure greater than 25 mm Hg, other significant, independent risk factors included an American Society of Anesthesiologists class of 2 or greater, and chronic renal insufficiency, analysis showed.

The study's design—a retrospective analysis based on the experience of a single, high-volume institution—was a limitation, Dr. Kaw said. In addition, "we did not have data regarding intraoperative factors, such as use of intraoperative nitrous oxide or vasopressors, blood loss, or type of anesthesia used."

He added that prospective studies are needed. ■

DATA WATCH



Medicare Covers Home Testing for Sleep Apnea

BY MARY ELLEN SCHNEIDER
Elsevier Global Medical News

Medicare officials have validated the use of certain home-based tests to diagnose obstructive sleep apnea.

The Centers for Medicare and Medicaid Services had previously established a national policy of covering continuous positive airway pressure treatment for beneficiaries with obstructive sleep apnea (OSA) if they are diagnosed using certain home sleep tests. But coverage for the tests themselves had been left to the discretion of the local contractor.

In the current decision memo, CMS officials noted that the evidence is "sufficient" to find that in appropriately selected patients, certain home testing monitors can identify a significant proportion of OSA patients who are likely to respond to treatment.

Under a final coverage decision issued in March, officials at the CMS opted to cover four categories of sleep testing devices when they are used to establish a diagnosis of OSA in a symptomatic patient.

THE COVERAGE OF A VARIETY OF HOME SLEEP TESTING DEVICES WILL GIVE MORE OPTIONS TO PATIENTS WHO HAVE NOT BEEN ABLE TO GET INTO A SLEEP LAB.

Type I tests must be performed in a sleep lab facility with an attendant. The other tests are covered if performed unattended in or out of a sleep lab facility or attended in a sleep lab facility.

The nationally covered tests include:

- Type I polysomnography, if performed attended in a sleep lab facility.
- Type II or type III sleep testing devices, if performed unattended in or out of a sleep lab facility or attended in a sleep lab facility.
- Type IV sleep testing devices measuring three or more channels, one of which is airflow, if performed unattended in or out of a sleep lab facility or attended in a sleep lab facility.
- Sleep testing devices measuring three or more channels that include actigraphy, oximetry, and peripheral arterial tone, if performed unattended in or out of a sleep lab facility or attended in a sleep lab facility.

"Medicare beneficiaries who have obstructive sleep apnea face significant risks for cardiovascular disease and other ailments," said Charlene Frizzera, CMS acting administrator. "This coverage decision establishes nationally consistent coverage and assures that beneficiaries who have sleep apnea can be appropriately diagnosed and referred for treatment."

The coverage decision is good news for the millions of Americans with undiagnosed and untreated sleep apnea, said Edward Grandi, executive director of the American Sleep Apnea Association based in Washington. The coverage of a variety of home sleep testing devices will give more options to patients who have not been able to get into a sleep lab, are not comfortable in a laboratory setting, or cannot afford the cost of an evaluation in a sleep lab, he said.

Mr. Grandi said he is hopeful that the CMS coverage decision will shift the focus away from how to properly diagnose obstructive sleep apnea and toward better treatment and continuity of care for the condition. "This is a step in the right direction," he said. ■

The decision memo is available at www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=227.

Dr. Peter C. Gay, FCCP, comments: *The ACCP Sleep Institute discussed this issue at some length during its January meeting. The general issue of portable monitoring has and continues to be controversial within the sleep community, and no consensus was reached. However, it was widely agreed that the original 1994 AASM classification scheme for portable testing did not anticipate nor is it adaptable enough to accommodate new and emerging technologies, such as those utilizing arterial tonometry and not measuring airflow. The recent decision memo from CMS dated March 3, 2009, essentially acknowledges the validity of these devices and accepts this technology as a unique classification.*

BRIEF SUMMARY
OF PRESCRIBING INFORMATION FOR
PROAIR® HFA (ALBUTEROL SULFATE)
INHALATION AEROSOL
For Oral Inhalation Only

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Bronchospasm

PROAIR HFA Inhalation Aerosol is indicated for the treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease.

1.2 Exercise-Induced Bronchospasm

PROAIR HFA Inhalation Aerosol is indicated for the prevention of exercise-induced bronchospasm in patients 4 years of age and older.

4 CONTRAINDICATIONS

PROAIR HFA Inhalation Aerosol is contraindicated in patients with a history of hypersensitivity to albuterol and any other PROAIR HFA Inhalation Aerosol components. Rare cases of hypersensitivity reactions, including urticaria, angioedema, and rash have been reported after the use of albuterol sulfate *[see Warnings and Precautions (5.6)]*.

5 WARNINGS & PRECAUTIONS

5.1 Paradoxical Bronchospasm

PROAIR HFA Inhalation Aerosol can produce paradoxical bronchospasm that may be life threatening. If paradoxical bronchospasm occurs, PROAIR HFA Inhalation Aerosol should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister.

5.2 Deterioration of Asthma

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of PROAIR HFA Inhalation Aerosol than usual, this may be a marker of destabilization of asthma and requires re-evaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids.

5.3 Use of Anti-inflammatory Agents

The use of beta-adrenergic-agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, e.g., corticosteroids, to the therapeutic regimen.

5.4 Cardiovascular Effects

PROAIR HFA Inhalation Aerosol, like other beta-adrenergic agonists, can produce clinically significant cardiovascular effects in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of PROAIR HFA Inhalation Aerosol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, PROAIR HFA Inhalation Aerosol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5.5 Do Not Exceed Recommended Dose

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

5.6 Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of albuterol sulfate, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema. The potential for hypersensitivity must be considered in the clinical evaluation of patients who experience immediate hypersensitivity reactions while receiving PROAIR HFA Inhalation Aerosol.

5.7 Coexisting Conditions

PROAIR HFA Inhalation Aerosol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after use of any beta-adrenergic bronchodilator. Large doses of intravenous albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.8 Hypokalemia

As with other beta-agonists, PROAIR HFA Inhalation Aerosol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

6 ADVERSE REACTIONS

Use of PROAIR HFA may be associated with the following:

- Paradoxical bronchospasm *[see Warnings and Precautions (5.1)]*
- Cardiovascular Effects *[see Warnings and Precautions (5.4)]*
- Immediate hypersensitivity reactions *[see Warnings and Precautions (5.6)]*
- Hypokalemia *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

A total of 1090 subjects were treated with PROAIR HFA Inhalation Aerosol, or with the same formulation of albuterol as in PROAIR HFA Inhalation Aerosol, during the worldwide clinical development program.

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

Adult and Adolescents 12 Years of Age and Older: The adverse reaction information presented in the table below concerning PROAIR HFA Inhalation Aerosol is derived from a 6-week, blinded study which compared PROAIR HFA Inhalation Aerosol (180 mcg four times daily) with a double-blinded matched placebo HFA-Inhalation Aerosol and an evaluator-blinded marketed active comparator HFA-134a albuterol inhaler in 172 asthmatic patients 12 to 76 years of age. The table lists the incidence of all adverse events (whether considered by the investigator drug related or unrelated to drug) from this study which occurred at a rate of 3% or greater in the PROAIR HFA Inhalation Aerosol treatment group and more frequently in the PROAIR HFA Inhalation Aerosol treatment group than in the matched placebo group. Overall, the incidence and nature of the adverse events reported for PROAIR HFA Inhalation Aerosol and the marketed active comparator HFA-134a albuterol inhaler were comparable.

Adverse Experience Incidences (% of Patients) in a Six-Week Clinical Trial*

Body System/Adverse Event (as Preferred Term)		PROAIR HFA Inhalation Aerosol (N = 58)	Marketed active comparator HFA-134a albuterol inhaler (N = 56)	Matched Placebo HFA-134a Inhalation Aerosol (N = 58)
Body as a Whole	Headache	7	5	2
Cardiovascular	Tachycardia	3	2	0
Musculoskeletal	Pain	3	0	0
Nervous System	Dizziness	3	0	0
Respiratory System	Pharyngitis	14	7	9
	Rhinitis	5	4	2

* This table includes all adverse events (whether considered by the investigator drug related or unrelated to drug) which occurred at an incidence rate of at least 3.0% in the PROAIR HFA Inhalation Aerosol group and more frequently in the PROAIR HFA Inhalation Aerosol group than in the placebo HFA Inhalation Aerosol group.

Adverse events reported by less than 3% of the patients receiving PROAIR HFA Inhalation Aerosol but by a greater proportion of PROAIR HFA Inhalation Aerosol patients than the matched placebo patients, which have the potential to be related to PROAIR HFA Inhalation Aerosol, included chest pain, infection, diarrhea, glossitis, accidental injury (nervous system), anxiety, dyspnea, ear disorder, ear pain, and urinary tract infection.

In small cumulative dose studies, tremor, nervousness, and headache were the most frequently occurring adverse events.

Pediatric Patients 4 to 11 Years of Age: Adverse events reported in a 3-week pediatric clinical trial comparing the same formulation of albuterol as in PROAIR HFA Inhalation Aerosol (180 mcg albuterol four times daily) to a matching placebo HFA inhalation aerosol occurred at a low incidence rate (no greater than 2% in the active treatment group) and were similar to those seen in adult and adolescent trials.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of PROAIR HFA. 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. Reports have included rare cases of aggravated bronchospasm, lack of efficacy, asthma exacerbation (reported fatal in one case), muscle cramps, and various oropharyngeal side-effects such as throat irritation, altered taste, glossitis, tongue ulceration, and gagging.

The following adverse events have been observed in postapproval use of inhaled albuterol: urticaria, angioedema, rash, bronchospasm, hoarseness, oropharyngeal edema, and arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles). In addition, albuterol, like other sympathomimetic agents, can cause adverse reactions such as: angina, hypertension or hypotension, palpitations, central nervous system stimulation, insomnia, headache, nervousness, tremor, muscle cramps, drying or irritation of the oropharynx, hypokalemia, hyperglycemia, and metabolic acidosis.

7 DRUG INTERACTIONS

Other short-acting sympathomimetic aerosol bronchodilators should not be used concomitantly with PROAIR HFA Inhalation Aerosol. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

7.1 Beta-Blockers

Beta-adrenergic-receptor blocking agents not only block the pulmonary effect of beta-agonists, such as PROAIR HFA Inhalation Aerosol, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic-blocking agents in patients with asthma. In this setting, consider cardioselective beta-blockers, although they should be administered with caution.

7.2 Diuretics

The ECG changes and/or hypokalemia which may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with non-potassium sparing diuretics. Consider monitoring potassium levels.

7.3 Digoxin

Mean decreases of 16% and 22% in serum digoxin levels were demonstrated after single dose intravenous and oral administration of albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving albuterol and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and PROAIR HFA Inhalation Aerosol.

7.4 Monoamine Oxidase Inhibitors or Tricyclic Antidepressants

PROAIR HFA Inhalation Aerosol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of albuterol on the cardiovascular system may be potentiated. Consider alternative therapy in patients taking MAO inhibitors or tricyclic antidepressants.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C:

There are no adequate and well-controlled studies of PROAIR HFA Inhalation Aerosol or albuterol sulfate in pregnant women. During worldwide marketing experience, various congenital anomalies, including cleft palate and limb defects, have been reported in the offspring of patients treated with albuterol. Some of the mothers were taking multiple medications during their pregnancies. No consistent pattern of defects can be discerned, and a relationship between albuterol use and congenital anomalies has not been established. Animal reproduction studies in mice and rabbits revealed evidence of teratogenicity. PROAIR HFA Inhalation Aerosol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In a mouse reproduction study, subcutaneously administered albuterol sulfate produced cleft palate formation in 5 of 111 (4.5%) fetuses at an exposure approximately eight-tenths of the maximum recommended human dose (MRHD) for adults on a mg/m^2 basis and in 10 of 108 (9.3%) fetuses at approximately 8 times the MRHD. Similar effects were not observed at approximately one-thirteenth of the MRHD. Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated subcutaneously with isoproterenol (positive control).

In a rabbit reproduction study, orally administered albuterol sulfate induced cranioschisis in 7 of 19 fetuses (37%) at approximately 630 times the MRHD.

In a rat reproduction study, an albuterol sulfate/HFA-134a formulation administered by inhalation did not produce any teratogenic effects at exposures approximately 65 times the MRHD *[see Nonclinical Toxicology (13.2)]*.

8.2 Labor and Delivery

Because of the potential for beta-agonist interference with uterine contractility, use of PROAIR HFA Inhalation Aerosol for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk. PROAIR HFA Inhalation Aerosol has not been approved for the management of pre-term labor. The benefit:risk ratio when albuterol is administered for tocolysis has not been established. Serious adverse reactions, including pulmonary edema, have been reported during or following treatment of premature labor with beta$_2$-agonists, including albuterol.

8.3 Nursing Mothers

Plasma levels of albuterol sulfate and HFA-134a after inhaled therapeutic doses are very low in humans, but it is not known whether the components of PROAIR HFA Inhalation Aerosol are excreted in human milk.

Caution should be exercised when PROAIR HFA Inhalation Aerosol is administered to a nursing woman. Because of the potential for tumorigenicity shown for albuterol in animal studies and lack of experience with the use of PROAIR HFA Inhalation Aerosol by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of PROAIR HFA Inhalation Aerosol for the treatment or prevention of bronchospasm in children 12 years of age and older with reversible obstructive airway disease is based on one 6-week clinical trial in 116 patients 12 years of age and older with asthma comparing doses of 180 mcg four times daily with placebo, and one single-dose crossover study comparing doses of 90, 180, and 270 mcg with placebo in 58 patients *[see Clinical Studies (14.1)]*. The safety and effectiveness of PROAIR HFA Inhalation Aerosol for treatment of exercise-induced bronchospasm in children 12 years of age and older is based on one single-dose crossover study in 24 adults and adolescents with exercise-induced bronchospasm comparing doses of 180 mcg with placebo *[see Clinical Studies (14.2)]*.

The safety of PROAIR HFA Inhalation Aerosol in children 4 to 11 years of age is based on one 3-week clinical trial in 50 patients 4 to 11 years of age with asthma using the same formulation of albuterol as in PROAIR HFA Inhalation Aerosol comparing doses of 180 mcg four times daily with placebo. The effectiveness of PROAIR HFA Inhalation Aerosol in children 4 to 11 years of age is extrapolated from clinical trials in patients 12 years of age and older with asthma and exercise-induced bronchospasm, based on data from a single-dose study comparing the bronchodilatory effect of PROAIR HFA 90 mcg and 180 mcg with placebo in 55 patients with asthma and a 3-week clinical trial using the same formulation of albuterol as in PROAIR HFA Inhalation Aerosol in 95 asthmatic children 4 to 11 years of age comparing a dose of 180 mcg albuterol four times daily with placebo *[see Clinical Studies (14.1)]*.

The safety and effectiveness of PROAIR HFA Inhalation Aerosol in pediatric patients below the age of 4 years have not been established.

8.5 Geriatric Use

Clinical studies of PROAIR HFA Inhalation Aerosol did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between 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 *[see Warnings and Precautions (5.4, 5.7)]*.

NETWORKS

Ped Pulmonology Task Force; Hopeful News on Lung Transplant

Pediatric Chest Medicine

The subspecialty of pediatric pulmonology was officially recognized by the American Board of Medical Subspecialties in 1984. Over the ensuing 25 years, pediatric pulmonologists have periodically addressed issues related to workforce and scope of practice.

In 1985, pediatric pulmonologists spent 50% of their time in clinical care, 25% in teaching, 15% in research, and 10% with administrative duties (*Pediatrics* 1988; 81:680). A more recent survey conducted as part of the Future of Pediatric Education Project (FOPE) of the American Academy of Pediatrics (AAP) showed that pediatric pulmonologists spent 70% of their time with clinical issues in the subspecialty and 14% of their time in nonclinical activities, such as research, teaching, or administration (Redding et al. *Pediatr Pulmonol* 2000; 30:190). Most practiced as part of a medical school group. The majority performed sleep studies, flexible bronchoscopy, and pulmonary function testing. Almost half of the patients cared for had asthma, and 20% had cystic fibrosis.

In the last several years, medical practices have changed. A new separate Board of Sleep Medicine requires anyone wishing to be certified in sleep medicine to take a second certifying examination. Distinctions between pulmonologists and allergists regarding the care of asthma patients have blurred. There is a separate subspecialty in pediatric critical care medicine; as such, the pulmonologist, who routinely renders outpatient care to a particular patient, is often relegated to the role of a consultant in the pediatric ICU.

The ACCP Pediatric Chest Medicine NetWork plans to form a task force to meet with members of the ATS Pediatric Assembly and the AAP Pediatric Pulmonology Section. The group will aim to redefine the role of a pediatric pulmonologist, to identify new areas of collaboration and opportunity, and to engage the newer members of the pediatric pulmonology society in the dialogue. A report of the task force will be produced for publication.

Dr. Howard Panitch, FCCP
NetWork Chair

Practice Administration—Get Involved!

The American College of Chest Physicians (ACCP) Practice Management Department, Practice Management Committee (PMC), Private Practice (PPN) and Practice Administration NetWorks (PAN) are working diligently to provide physicians and administrative members with information and resources they need to help improve the overall performance of their practice(s). The success of the NetWorks and of ongoing practice management initiatives relies on members to become involved in the process! Here's what you can do:

- Encourage your physician or administrative leader to join the College and become an active member of the Practice Administration NetWork. The benefits of networking with national experts and colleagues are invaluable to your practice and professionally rewarding to any leader.
- Take part in the annual **Practice Profiles Survey**. In return for your 2009 participation, you will receive: a complimentary report comparing your practice to others in chest medicine; and complimentary copies of the MGMA's "Cost Survey Report" and/or "Physician Compensation and Production Survey Report" in print format.
- Plan to attend CHEST 2009 in San Diego to increase your practice management acumen, dialogue with colleagues from around the country about the challenges in health care today, and take home a few pearls that may improve your bottom line.

To get involved, please contact Marla Brichta, Assistant Vice President of Health Affairs, at (847) 498-8364.

John Bauer, MBA, CPA, FACMPE, and
Kim French, MHSA, CAPPM

Transplant

Improved perioperative management has led to improved short-term survival after lung transplantation. However, acute and chronic rejection are common and lead to poor long-term outcomes. In addition, despite recent increases in the utilization of donors and lung transplants performed, only a minority of donor lungs are utilized. As a result, approximately 250 patients waiting for lung transplant in the United States die before receiving one.

This article will briefly describe two techniques that can potentially ameliorate these problems. First, in a report from Dr. Machiarini and his team in Barcelona (*Lancet* 2008; 372:2023), a successful airway transplant without immunosuppression was performed. A 30-year old woman with left bronchial stenosis received a left bronchial transplant from a cadaveric donor. The donor bronchus was decellularized completely, and stem cells from the recipient were obtained and induced to grow as chondrocytes and epithelial cells. The cells were placed on the bronchial tissue, and, after 4 days, the graft was transplanted. The patient has received no immunosuppression and is doing well 4 months after the procedure.

The second report comes from the University of Toronto (Cypel et al. *J Heart Lung Transplant* 2008; 27:1319). Donor lungs that were originally considered unsuitable for transplant were improved, and then transplanted. The 56-year-old patient was extubated 2 days after the operation and was discharged home 2 weeks later. The lungs were perfused with a solution that consisted of a synthetic oxygen-carrying solution, dextran, saline solution, and anti-inflammatory compounds; all cells were removed prior to perfusion of the lungs, which were maintained in normal temperatures. This technique could significantly increase the number of transplants in the short-term.

Dr. Denis Hadjiliadis, FCCP
NetWork Vice-Chair

This Month in *CHEST*: Editor's Picks

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

- **Specific IgE Response to Trichophyton and Asthma Severity.** *By Dr. H. Matsuoka, et al.*
- **Trichophyton Asthma**. *By Dr. T. A. E. Platts-Mills, and Dr. J. A. Woodfolk. (Invited Editorial)*
- **Incidence and Risk Factors for Venous Thromboembolic Disease in Podiatric Surgery**. *By Dr. A. H. Felcher, et al.*
- **Despite Decreased Wait-List Times for Lung Transplantation, Lung Allocation Scores Continue To Increase.** *By Dr. A. Iribarne, et al.*

TRANSPARENCY IN HEALTHCARE

- **Physician Staffing Models and Patient Safety in the ICU.** *By Dr. O. Gajic, FCCP, and Dr. B. Afessa, FCCP.*

CONSENSUS STATEMENT

- **ACCP/SRLF Statement on Competence in Critical Care Ultrasonography.**

CONTEMPORARY REVIEWS IN CRITICAL CARE MEDICINE

- **Evaluation of Pain in ICU Patients.** *By Dr. K. Puntillo, et al.*
- **Pain Management Principles in the Critically Ill**. *By Dr. B. L. Erstad, et al.*

www.chestjournal.org

Pulmonary Perspectives

Bronchoscopy: A Need for Standards, Quality Improvement, and Databases

Improving the quality of health-care delivery has become a focal point of recent discussions. The Institute of Medicine report in 2000 initiated a discussion around mistakes that might result in significant avoidable loss of life during diagnosis and treatment of illnesses. Additionally, it is lamented that the percentage of the US gross domestic product spent on health care ranks highest in the world but that the quality of care delivered may not reflect the amount of financial effort.

The discussion about improving safety and quality since then has been in full swing, and multiple interventions and disease management approaches have been evaluated for possible inclusion in a catalog of specific outcome and quality control measures.

Obviously, the discussion about connecting the level of payment for a procedure to a desired outcome is also well underway and has become a clear mandate by the Centers for Medicare and Medicaid Services (Rosenthal. *N Engl J Med* 2007; 357:1573).

Bronchoscopy is a procedure that is very commonly performed and is often considered to be a defining intervention for a chest physician. Several attempts have been made to standardize training requirements for pulmonologists, but quality control, standards, and bronchoscopic procedures have not yet been properly connected. This seems curious, as the procedure is widely used and with its defined outcomes and limited performance parameters certainly would be relatively easy to assess and follow. One of the reasons may be that conventional bronchoscopy, such as a bronchoalveolar lavage (BAL), is such a safe procedure that adverse events occur with such low frequency, that quality control mechanisms for procedure performance would make little sense. On the other hand, it is very difficult to assess if the original indication for a BAL in the ICU was truly indicated, therefore, making such quality assessments too difficult to use in everyday practice.

Times have changed. Bronchoscopy has grown from a simple diagnostic procedure to one that can employ multiple new tools for diagnosis, for example, endobronchial ultrasound. More complex bronchoscopy may experience a significant increase in use, such as use in more primary cancer staging and primary diagnosis of peripheral lesions. As this use grows, so does the opportunity and need for outcomes and quality control. The same holds true for more advanced therapeutic procedures, such as stenting or, in the future, maybe endobronchial lung volume reduction.

BRONCHOSCOPY HAS GROWN FROM A SIMPLE DIAGNOSTIC PROCEDURE TO ONE THAT CAN EMPLOY MULTIPLE NEW TOOLS FOR DIAGNOSIS.

In a recent issue of *Chest* (Ernst et al. *Chest* 2006;134: 514), we presented an early attempt of establishing an outcomes database for advanced therapeutic procedures. In this multi-institutional effort (Henry Ford Hospital in Detroit [Dr. Michael Simoff, FCCP], New York University Hospital in New York [Dr. David Ost, FCCP], Thoraxklinik Heidelberg in Germany [Dr. Felix Herth, FCCP], and BIDMC in Boston [Dr. Armin Ernst, FCCP]), prospective predefined data were collected and analyzed. In this database, parameters, such as indications, resource use, and specific outcomes for individual procedures, are assessed with a detailed description of morbidity and mortality.

We found the introduction of such a database into clinical routine to be easy and the information obtained to be very useful. Another database in development is for the "lesion-specific" outcome of advanced diagnostic procedures: for all bronchoscopic needle aspirations or transbronchial biopsies, the endoscopic adjuncts used and the characteristics of the targets are recorded. This will allow for benchmarks to be established, so one can assess what a yield should be, for example, for a 12-mm lymph node in 4R position with a specific diagnostic approach. For safe diagnostic procedures, a simplified collection of morbidity and mortality data obviously makes more sense.

Databases such as these can serve many purposes (Agency for Healthcare Research and Quality [AHRQ], Publication Number 07-EHC001-1) (www.effectivehealthcare.ahrq.gov): they can be used to objectively assess resource and time use, being a better negotiation tool for reimbursement. Outliers can be identified and, if they are on the undesirable side, education measures can be instituted so that the procedures can be improved and safety and quality, therefore, will improve. Of particular interest in these databases is the opportunity to identify the "best performers"—the individuals who achieve the best results with the fewest resources used and try to identify specific opportunities that can be used for a broader base. The goal is to improve general health-care quality, as well as delivery.

Databases can also be used for recertification purposes. They may be tied into a larger recertification process, and demonstrating certain standards, especially if it happens in real time, could be used in the process.

On a health-care economics side, these databases can be exceedingly useful. As stated above, the cost of health care is exploding and the exponential introduction of new technologies is frequently blamed, since none of them ever present a cost savings. Unfortunately, no definitive process exists for structured health technology evaluation in which a rigorous comparison of new technology against established standards occur (www.cbo.gov/ ftp docs/88xx/doc8891/12-18-comparative-effectiveness.pdf).

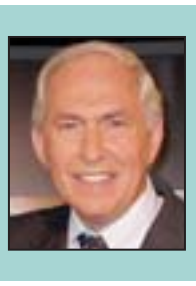
Even though there is a lot of movement to establish such a federal agency, it may be a long time until we see it. In the meanwhile, procedural databases can be used to extract data comparing operators using newer or more expensive technologies against operators using more established technologies for the same indications—a potential tremendous positive impact on quality and heath-care costs.

The elephant in the room is the push to tie reimbursement to quality and outcomes, also known as pay-for-performance. A full discussion of the pros and cons of this approach is beyond the scope of this article, but it seems clear that this will be part of every health-care provider's life. Physician-driven databases do offer a chance to participate in this discussion with objective data and, most importantly, with data that we as physicians feel are important and truly provide benefit. The other option is to wait and see what data one will be required to report—not a desirable outlook.

The ACCP recently initiated a pilot program called AQuIRE (ACCP Quality Improvement Registry, Evaluation, and Education). The AQuIRE Registry is designed to assist the chest physician to meet increasing demands placed upon them by the public, credentialing bodies, regulatory agencies, payers, and the institutions in which they practice. The AQuIRE Registry will also serve as a tool to collect de-identified patient data for measurement of provider performance and technology assessment.

Diagnostic and Therapeutic Bronchoscopies are the first of the AQuIRE Registry's two clinical modules. These clinical modules are currently being beta tested at 10 centers and practices until early 2010 and then are scheduled for release to the general physician public. This represents a much-needed start into the future of health-care delivery with data-supported decision making, opportunities to benchmark real-time, provide a better overview of intelligent resource use, and, as a result, offer the best possible health care to our patients.

To find acceptance, database maintenance must be relatively simple, should happen in real-time, and be embedded into other processes, such as certification, training, quality improvement initiatives, and, in the future, billing. A Web-based service, as with AQuIRE, that allows for all these functions to come together is the most desirable solution. ■



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PCCU Lessons for April

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PCCU
Pulmonary and Critical Care Update

- **Asthma Treatment: Step-Down and As-Needed Use of Inhaled Corticosteroids**
  By Dr. Paul M. O'Byrne, MBBCh, FCCP
- **Managing the Critically Ill Pregnant Patient**
  By Dr. Margaret A. Miller; and Dr. Ghada Bourjeily, FCCP

DR. JAMES A. L. MATHERS, JR., FCCP

PRESIDENT'S REPORT

ACCP Outlines Agenda for 2009

The divisions of the College have been busy establishing the program for CHEST 2009, reviewing multiple requests for endorsement of position papers and statements from our sister societies, and intervening with regulatory bodies on behalf of our members.

I have recently returned from the annual meeting of the Society of Critical Care Medicine (SCCM), where ACCP leadership and staff had the opportunity to meet with the representatives of the American Thoracic Society (ATS), American Association of Critical-Care Nurses (AACN), and SCCM to discuss mutual interests.

We were able to address many issues relevant to the daily activities of our membership and are developing collaborative approaches with recommendations for constructive solutions.

We have submitted joint comment letters addressing the activities of the Recovery Audit Contractors, the Institute of Medicine (IOM) recommendations on resident duty hours, CMS' position on hospital-acquired infections, ABIM requirements for training programs in sleep, and CMS efforts to establish CPT coding for home sleep studies.

Recovery Audit Contractors

One of our most pressing issues in clinical practice involves the expansion of the Recovery Audit Contractor program. This program is becoming a burden to physicians providing patient care, and ACCP has signed an AMA coalition letter opposing the expansion sent to the Acting Administrator, CMS, on February 27.

There is widely acknowledged imprecision associated with chart audits, as the broad parameters for reporting E&M codes do not lend themselves to basic review. An external review of a physician's coding requires that all factors, including multiple diagnoses, variations in age, and the complexity of decision-making, are considered and carefully evaluated.

Despite detailed Medicare guidelines that specify the documentation required for each level of E&M service, knowledgeable individuals often reach different conclusions regarding the E&M level of service justified by the documentation. These problems are further exacerbated by the fact that individuals performing the audits are not physicians of the same specialty and state as the physicians being audited. We are aware that even experienced reviewers may disagree on the most appropriate code to describe a particular service as described in a medical record. The shifting Medicare rules pertaining to the documentation and coding of consultations just adds to the confusion. We have strongly stated in our letter that we believe it is unreasonable for CMS to allow the Recovery Audit Contractors to review consultations and penalize physicians for minor variations in charting.

We firmly believe that the best way to reduce common billing and coding mistakes is through targeted education and outreach, rather than onerous audits performed by outside contractors with incentives to deny claims.

Resident Duty Hours

After careful review of the recently released IOM report and recommendations on resident duty hours, the SCCM, ATS, ACCP, and the AACN have communicated to the Chief Executive Officer, Accreditation Council for Graduate Medical Education (ACGME), their opposition to the IOM recommendation to apply further, more sweeping resident duty hour restrictions.

We have pointed out that the studies referenced in their report focus on interns, and neither the ACGME nor the IOM have differentiated level of training as applied to duty hours. There is no recognition that the educational focus of an intern is quite different from a second- or third-year fellow.

Similarly, there is no recognition that the responsibilities of an on-call intern are very different from a second- or third-year fellow.

It is our opinion that continuity of care, especially for those patients who are critically ill, is essential to understanding the management and impact of care for a specific disease and patient. Further restrictions of duty hours will increase the frequency at which resident trainees and fellows must leave a critically ill patient whose condition may change frequently and could jeopardize that continuity.

Particularly important is our belief that further restrictions of duty hours may also impact negatively the competency of trainees in early recognition, resuscitation, and stabilization of the critically ill patient, where these skills and the judgment of when to apply these skills are best acquired over time in a patient care setting, oftentimes at night.

It is the group's opinion that without evidence demonstrating benefit and without advanced planning to determine if optimal resources, methods, personnel, and scheduling are in place to maximize the training of new specialists and subspecialists, it is ill-advised to impose additional duty hour restrictions on these trainees.

Hospital-Acquired Infections Workgroup

In June 2008, NAMDRC was invited to meet with Dr. Thomas B. Valuck, Medical Officer and Senior Advisor, Center for Medicare Management at the Centers for Medicare and Medicaid Services (CMS) regarding the societies' position on the CMS proposed rule for hospital-acquired conditions. Phil Porte, NAMDRC CEO, invited the ACCP, ATS, AACN, and SCCM to attend with him. We did send representation to that meeting held June 6.

Based on this meeting, a joint comment letter from the five societies was submitted on June 13, 2008, detailing our view that not all hospital-acquired conditions are preventable.

We focused on four specific areas: ventilator-associated pneumonia (VAP), iatrogenic pneumothorax, deep vein thrombosis/pulmonary embolism, and delirium in the critically ill.

The ACCP and ATS were subsequently invited to a related Centers for Disease Control and Prevention conference on health-care-associated infections held on September 25, 2008. We were represented by Drs. Neil MacIntyre, FCCP, Jonathan Truwit, FCCP, and Richard Wunderink, FCCP.

WE BELIEVE IT IS UNREASONABLE FOR CMS TO ALLOW THE RECOVERY AUDIT CONTRACTORS TO PENALIZE PHYSICIANS FOR MINOR VARIATIONS IN CHARTING.

Based on this meeting, CMS issued a proposed rule for preventing health-care-associated infections on January 6, 2009. We were pleased that Health and Human Services, in response to our input, made the decision to focus on process measures to reduce the incidence of VAP rather than using this vague entity as a never event.

The original five societies—ACCP, ATS, NAMDRC, SCCM, and AACN—submitted a letter in response to these recommendations on February 6, 2009. We are recommending that CMS participate in the development of a plan to address the complex issue of VAP.

We have proposed the formation of a "VAPnet," equivalent to the ARDSnet, to study and provide additional data on this topic.

As an initial step, the leadership of The Critical Care Workforce Partnership (ACCP, ATS, AACN, and SCCM), along with NAMDRC, has decided to establish the Hospital-Acquired Infections Collaborative (HAI-C) to interact with federal agencies addressing the issue of hospital-acquired infections. This group will be participating in an upcoming FDA/IDSA-sponsored meeting to address VAP. The group will also be applying for a NIH conference grant to further a collaborative approach to this important issue. The ACCP will provide the initial staff support, and Dr. Wunderink will become the first chair of this collaborative.

Sleep Medicine Training in Pulmonary Fellowships

Recognizing the multidisciplinary nature of the practice of sleep medicine and the diverse training backgrounds and career goals of the physicians entering this field, the ATS Training Committee has recommended modifications in the ACGME's Sleep Medicine Fellowship Training Program requirements and provided these recommendations to the ACCP for comment.

The College has endorsed the recommendations that the current ACGME requirement for "12 months of continuous clinical training" in sleep medicine be changed to an "equivalent of 12 months of training obtained over the course of not more than four years." We have recommended that the joint training in pulmonary/critical care and sleep medicine be only available to those programs with accreditation in training for all three disciplines.

We have mandated that vacations, on-call requirements, and conferences are not scheduled to compromise any one component of training.

We have suggested a separate program director for pulmonary/critical care medicine and for sleep medicine to ensure that no one component will be overlooked. These program directors would be both responsible and accountable for the trainees in ensuring that they meet all requirements.

Home Sleep Studies

Several details remain to be clarified under the recent Medicare approval of home sleep studies.

The ATS, ACCP, and NAMDRC are reiterating support of home sleep studies and working together to ensure the establishment of proper CPT codes. We want to be sure that the final policy is very clear that both facility-based and home sleep studies are covered when medical necessity exists, and the prescribing physician has determined that the diagnostic test of choice is clinically indicated.

We have recommended that the policy include guidelines as to when in-laboratory testing should be performed and reimbursed when a portable monitor study in a symptomatic patient is negative or nondiagnostic. There is good evidence to support an expected failure rate in excess of 10% using home sleep apnea testing (HSAT). If HSAT results conflict with the clinical findings, then repeat testing of the treating physician's choice should not be considered duplicative.

Flexibility for providers in ordering an appropriate second study, whether it is another home sleep apnea test or a full polysomnogram, should be left to the discretion of the clinician.

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Pulmonary Rehabilitation Benefit Under Medicare

As you are probably aware, pulmonary rehabilitation was established as a Medicare benefit by legislation at the end of the 110th Congress.

Our Practice Management Committee, CPT advisors, NAMDRC, and American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) have been working together for many months on the development of new CPT codes for pulmonary rehabilitation. The goal is to create codes that accurately describe the practice, are valued appropriately, and match the newly defined benefit in the Coverage Determination of CMS.

We are about to submit a letter to CMS in collaboration with ATS, NAMDRC, and AACVPR. We believe there are two practical options to develop a coding structure to report pulmonary rehabilitation services. One option is to augment the existing G-codes for pulmonary rehabilitation. Another option is to remove the existing CMS restriction on the physical medicine codes to allow other health-care professionals to use these physical medicine codes to report pulmonary rehabilitation services.

We have requested a meeting with CMS to explore these options further.

Critical Care Research Agenda

As a member of the Critical Care Workforce Partnership (CCWP), the ACCP is contributing to position statements and action plans to help define the national research agenda for critical care medicine. A number of opportunities to work with other organizations, the NIH, and Agency for Healthcare Research and Quality (AHRQ) have opened up.

The USCIIT Group (US CC Trials Steering Group), initiated by Dr. J. Perren Cobb, seeks to be the most inclusive network of critical illness and injury clinical investigators in the United States, including most, if not all, of the critical illness and injury clinical specialties. The group currently includes representatives from five NIH Institutes, including the NHLBI. The mechanism that funds the USCIIT Group is an NIH cooperative partnership grant. The goal is to create a strategic plan for critical illness and injury clinical research in the United States.

As a follow-up to COMPACCS, FOCCUS, and PROMIS, Dr. David Ingbar, FCCP, past president of ATS, has proposed an ambitious undertaking for the CCWP. In spite of the information delivered in these publications, a framework or consensus on the agenda for critical care research in the United States has not evolved. The goal of this collaborative "Quad Society" project would be to define a broad, comprehensive agenda for critical care research that is of importance to health care in the United States. It is envisioned that this would interdigitate with the USCIIT efforts, and Dr. Cobb has proposed that the USCIIT Group grant and meeting format could facilitate the strategic plan workshop to initiate the CCWP project.

The three presidents initiative—Dr. Kay Guntupalli, FCCP; Dr. Mitchell Levy, FCCP; and Dr. Randy Curtis, FCCP, have proposed an ACCP-SCCM-ATS task force to facilitate the integration of evidence-based medicine, protocols, and quality measures into the practice of critical care medicine. This is to be an effort to conform to "best practices," reduce practice variation, and, at the same time, respond to individual patient variation and individual needs of critically ill patients and their families. Integration of these competing perspectives offers an opportunity to advance research and clinical care in critical care medicine.

The CCWP legislation promoted by ACCP and introduced in the 110th Congress has expired. Part of this legislation requested funds for AHRQ to study the use of telemedicine in the ICU setting. Recognizing the potential of advanced technology to improve patient care, the CCWP approached AHRQ last fall with a proposed ICU telemedicine project and was met with a favorable response. This will be a three-component project.

- A national survey study will be conducted by the four societies to understand the current barriers and facilitators to implementation of telemedicine in the ICU setting.
- An AHRQ-sponsored workshop to be organized by the four societies and held at AHRQ campus for the purpose of identifying the state of the science in delivery of telemedicine in the ICU, including effects on patient safety, quality of care, and costs of care and defining the important future directions for research in these areas.
- Based in part on the workshop report, AHRQ will develop a request for proposals for research to identify and evaluate comparative effectiveness of strategies for conducting telemedicine in the ICU.

These are just a few of the activities in which your ACCP leadership and staff are actively involved. Working together with our sister societies, we are building relationships with federal agencies and making progress in influencing the rules and regulations that affect our ability to care for our patients in the most clinically appropriate manner. For more information on these and other activities, please see "Practice and Advocacy" on the ACCP Web site at www.chestnet.org. ■

Critical Care Commentary

Perioperative Fluids

**"Water, water, everywhere.
Nor any drop to drink."**
Samuel Taylor Coleridge, "The Rime of the Ancient Mariner," 1797

Perioperative fluid therapy remains controversial. Should we give more fluids? Fewer fluids? What is indicated and when? Can we influence outcome or is that already determined by the patient's condition? And, there are many studies that have emphasized and refuted all these points. So, what should the perioperative physician do?

Critical review of clinical trials reveals that current standard fluid therapy is hardly evidence-based and has been challenged for years (Van der Linden. *Acta Anaesthesiol Belg* 2007; 5894:245). Indeed, some 90 years ago, Cannon pointed out that administration of fluids before operative control of an injury was ineffective (Cannon et al. *JAMA* 1918; 47:618). Bickell emphasized the benefit of surgical correction before resuscitation, which could blow out a soft clot (Bickell et al. *J Trauma* 1989; 29:409). But during both the Korean and Vietnam war campaigns, large fluid volume resuscitation was advised to maintain renal perfusion (and the da Nang lung was born). Was rational thinking starting to lose ground or would the kidney survive?

Tradition has taught us that there are three fluid spaces. The first is recognizable as the intravascular space. The second is neither as well defined nor as quantified but is considered to be interstitial and extravascular spaces, where fluid accumulates either normally or in response to injury or edema formation. Fluid shifting is ongoing and can obscure hypovolemia or overload. Also, the vascular beds can undergo dramatic capacitance changes secondary to anesthetic drugs and pathologic states. But where is this third space?

Dr. Neil Halpern, FCCP
Section Editor, *Critical Care Commentary*

Almost 50 years ago, two groups of patients were studied to try to more closely understand the acute changes that determine the perioperative management of fluids and electrolytes (Shires et al. *Ann Surg* 1961; 154:803). The control group consisted of 5 patients undergoing minor surgery with general anesthesia, and the second group (13 patients) had elective major surgical procedures. Plasma volume, RBC mass, and extracellular fluid volumes were measured in all patients on two occasions during the operative period by using iodine 131-tagged serum albumin, chromate 51 RBCs, and sulphur 35-tagged sodium sulphate. Anesthetics used included pentothal, cyclopropane, trilene, ether, and nitrous oxide. Major surgeries were cholecystectomy, gastrectomy, and colectomy.

Based on a decrease in functional extracellular fluid in group 2, the authors concluded that there was internal redistribution (that is, the third space was discovered), which should be made up by fluid administration. The findings were "confirmed" in an exsanguinated dog model that did better with immediate fluid rather than blood replacement (Shires et al. *Arch Surg* 1964; 88:688).

Arguing against this "logic," Moore postulated that a metabolic response to surgical stress caused sodium and water retention, and perioperative fluid restriction was indicated (Moore. *N Engl J Med* 1958; 7:325; 1958; 8:377; 1958; 9:427). The debate even prompted an editorial by the two combatants, which urged moderation (Moore et al. *Ann Surg* 1967; 166:300).

But the former doctrine appears to have won. Protocols calculated deficits based on degree of trauma, insensible losses, and a host of other "variable" fluid decreases, all of which were to be replaced with crystalloids. Every house officer can repeat the 4:2:1 "rule," found in all major textbooks, where it appears with gospel-like intonation, although without reference (0-10 kg requires 4 mL/kg; 11-20 kg, 2 mL/kg; and >21 kg, 1 mL/kg. However, I did read in the "Bible of Anesthesia" that the "rule" "segments the curvilinear relationship between body weight and metabolic rate into three linear parts" (Tonnesen. Crystalloids and colloids in anesthesia. 4th ed. New York: Churchill Livingstone, 1994; 1598). What exactly that means escapes me. If water requirements are proportional to metabolic rate, and if basal metabolic rate is related to body surface area, then, surely, formulae should take into account neurologic, endocrine, and cardiovascular status. What currently guides us is too simplistic.

There is the concept of preoperative dehydration, too. Are patients so dehydrated when they arrive at the hospital at 7:00 AM after having fasted for 8 h that they require some 1,500 to 2,000 mL of fluid (that is 6 to 8 cups of coffee) within the first 1 to 2 h of surgery and, perhaps, a total of 3 to 5 L over 4 to 5 h, especially if there is a 2-unit blood loss? A poll of our anesthesia staff indicated that while many insert IV cannulae and give lots of fluids, by 10:00 AM, their average intake of coffee/tea/juice is 240 mL plus or minus 240 mL. And the staff was not in a metabolic coma. Why, then, should our patients need so much fluid?

Several studies suggest that fluid resuscitation may be over generous and even contribute to complications (Joshi. *Anesth Analg* 2005; 101:601). Patients who developed postoperative blindness after lumbar surgery also had a very large positive fluid balance. Could restricting IV fluids then be beneficial? Comparing the standard administration of greater than 3 L water with 154 mmol sodium per day and restricted less than 2 L water and 77 mmol sodium intake after hemicolectomy indicated significantly more complications in the standard group. There were significant reductions in solid and liquid phase emptying times in the study group, reducing postoperative ileus (Lobo et al. *Lancet* 2002; 359:1812).

Intravenous crystalloids remain in the intravascular space for very short periods, redistributing quickly to soft and damaged tissue and dependent areas, such as the gut, lungs, and laryngeal areas. Edema in the gut wall increases the inflammatory response and retards forward movement. A more serious complication is abdominal compartment syndrome, causing respiratory and renal dysfunction and increased epidural bleeding during spine surgery (McNelis et al. *Arch Surg* 2002; 137:133). Excessive crystalloids also cause coagulation abnormalities and increased cutaneous edema delays wound healing (Holte et al. *Br J Anaesth* 2002; 89:622). Moreover, patients go home from a short hospital stay 10 to 20 pounds heavier after having had a part removed!

In commenting on these studies, I would try to distill what we have. We were all warned that hetastarch should be avoided because it causes bleeding, although, it stays in the intravascular space some 20 times longer than crystalloid. Indeed, it may induce a hypocoagulable state. But is that so awful, given

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that a major complication of surgery and hospitalization is deep venous thrombosis, and many of our protocols are aimed at avoiding this problem and its consequences? Crystalloids have been shown to produce a hypercoagulable state at 20 to 40% dilution, whereas lower molecular weight hydroxyethyl starches and colloids in suspended salt solutions exert minimal coagulation derangements (Roche et al. *Anesth Analg* 2006; 102:1274).

The tetrastarches, hydroxyethyl starch 130/0.4, recently approved in the United States, have been shown to represent a substantial advance in colloid therapy, offering good volume replacement with a low risk of side effects (James. *Curr Opin Anaesthesiol* 2008; 21:674). They have also been proven superior (and cheaper) over albumin for volume replacement in children undergoing cardiac surgery (Hanart et al. *Crit Care Med* 2009: e-pub ahead of print). Particularly convincing of the superiority of colloids for perioperative fluid replacement is the ability of hydroxyethyl starch to improve tissue oxygen tension significantly more than crystalloids (Lang et al. *Anesth Analg* 2001; 93: 405), indicating improved microperfusion and less endothelial swelling.

The message is that we need to restrict and reevaluate perioperative fluid management (Chappell et al. *Anesthesiology* 2008; 109:723). Preoperative volume loading is not necessary in most cases. The classic third space does not exist. Crystalloid overload is bad. Routine replacement of insensible losses is to be eschewed. Demand-related regimens should be followed to improve patient outcome. Perioperative fluid shifting must be minimized. Fluid balance should be maintained. Inappropriate IV fluid therapy is a significant cause of patient morbidity and mortality and, in most uncomplicated cases, a restrictive approach appears preferable (Hilton et al. *Med J Aust* 2008; 189:509).

But given the enormous variability of the patient, his or her condition, and the perioperative parameters, a means to assess what exactly meets appropriate fluid replacement is still lacking. The intravascular space is not static. The esophageal Doppler, supplying continuous real time objective data, may well emerge as the monitor of preload conditions and help us manage cardiac contractility and the effect of afterload impedance on left ventricular performance (CMS Decision Memo File CAG-00309R, May 22 2007; Chytra et al. *Crit Care* 2007; 11[R24]:1). Our time-honored protocols could soon blow in the wind. ■

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CHEST 2009—Surf's Up!

CHEST 2009 is just 6 months away in San Diego, California. A little Internet surfing done now can enhance your experience later. Opportunities related to CHEST 2009 are currently available, and you can take advantage of them online. Be sure to check out:

▶ **Call for Abstracts.** Submit abstracts of your original investigative work for presentation at the meeting. Accepted abstracts will be eligible for investigative awards. Submission is free at www.chestnet.org. Submission deadline: May 4.

▶ **Call for Case Reports.** ACCP affiliate members are invited to submit case reports for presentation at the meeting. Accepted cases will be eligible for awards. Submission is free at www.chestnet.org. Submission deadline: May 4.

▶ **The CHEST Foundation Awards.** The CHEST Foundation will confer more than $600,000 in awards for clinical research, leadership, and pro bono service. Check your eligibility and apply at www.chestfoundation.org.

Application deadline: April 30.

▶ **CHEST Challenge.** ACCP affiliate members can compete to win a free trip to CHEST 2009 and cash prizes by playing CHEST Challenge, an online contest related to pulmonary, critical care, and sleep medicine. Get your game on at www.chestnet.org. Game ends: May 31.

Now is also the time to surf www.sandiego.org to take a virtual tour of San Diego. Known for its idyllic year-round climate, pristine beaches, and dazzling array of attractions, San Diego appeals to visitors of all ages from around the world. With so many options available, you might have a hard time deciding what to do in your free time. Narrow down your choices now by visiting San Diego's Web site.

CHEST 2009 will be held from October 31 through November 5. Watch for special celebrations and events that will be happening as the ACCP celebrates 75 years of inspiring leadership, education, clinical practice, and communication. CHEST 2009 registration is open now, and early registration discounts will be offered through August 31. Learn more about the meeting and register at www.chestnet.org. ■

Foundation Awards' Deadline Nears, Children's Poster Contest Underway

Still Time To Apply for 2009 Awards

Take advantage of a valuable benefit of ACCP membership, and submit an application for one of The CHEST Foundation awards offered in 2009. All applications and supporting documents must be postmarked April 30, 2009, or earlier, to be considered for a 2009 award.

If your work focuses on critical care, lung cancer, women's health, COPD and ATT deficiency, leadership in end-of-life care, or treating the geriatric patient in chest-related medicine, then consider applying for a 2009 award.

The new D. Robert McCaffree, MD, Master FCCP Humanitarian Awards offer ACCP members involved in pro bono service the opportunity to apply for a $5,000, $10,000, or $15,000 award to the nonprofit or nongovernmental organization that supports their pro bono work.

Go to www.chestfoundation.org for more details and an opportunity to apply online for most of the 2009 awards.

The CHEST Foundation's Ambassadors Group

CHEST 2009 Poster Contest Is Underway

If you have a creative child, grandchild, niece, or nephew who loves to draw and is 8 to 14 years old, the Ambassadors Group asks that you encourage them to enter the CHEST 2009 Poster Contest. Entries need to focus on the theme of "Love Your Lungs," be on 8 ½" x 11" white paper, and not include any photographs or computer drawings. For vivid color, magic markers are recommended. All words on the poster must be in English. Entries are judged based on the use of color, unique design, and effective way of communicating the theme of "Love Your Lungs."

Please mail entries to the attention of Sue Ciezadlo at The CHEST Foundation before the deadline of June 1, 2009, and include the required submission form signed by parent, grandparent, aunt, or uncle. For more information and a submission form, go to The CHEST Foundation's Ambassadors Group Web page, which is located at www.chestfoundation.org/specialInitiatives/ambassadors-Group.php. ■

ACCP

CHEST 2008 poster contest winning entry.

Product of the Month: A Physician's Perspective®

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A Physician's Perspective® provides expert reviews, opinions, and highlights on clinical information relevant to the chest professional health-care community. This monthly wide-reaching resource presents various hot-topic medical issues relevant to your clinical practice and the care you provide to your patients. The information is provided through the collective efforts of the ACCP Education, Health and Science Policy, and Quality Improvement Committees. Embedded within each month's clinical topic focus are links to other relevant information that can be found throughout ACCP, CHEST Foundation, and *CHEST* journal resources.

We trust this new educational medium will prove useful and also serve as a catalyst for you to share your innovative ideas, opinions, and challenges faced within your own medical community. This resource is fun and collaborative. Additional interactive activities, including chest quizzes, clinical case puzzlers, and prizes for those who participate, will all lead up to other opportunities available at the CHEST annual meeting. We look forward to your participation, your responses, and your reactions.

Enjoy the monthly activities and resources offered within A Physician's Perspective®, available exclusively from the ACCP. ■

CLASSIFIEDS

Also available at www.elsevierhealthcareers.com

PROFESSIONAL OPPORTUNITIES

Marietta Pulmonary Medicine Suburban Atlanta

Well-established, busy 11-physician single-specialty Pulmonary practice in suburban Atlanta, Georgia, looking for one or more BC/BE Pulmonary/Critical Care physicians. Sleep certification is a plus. Practice includes all aspects of pulmonary medicine, including critical care, sleep medicine, out-patient clinic, pulmonary rehab and clinical research. Practice located at two large acute-care hospitals, with one being the busiest ER in Georgia, and also rounds at a near-by long term acute care hospital. Competitive salary with bonus potential, generous benefits package and malpractice coverage. Fax CV to: 770-792-1738.

Pulmonary Critical Care Physician

Connecticut – Pulmonary Critical Care Physician needed to replace a relocating physician. Approximately 50% inpatient, 50% outpatient practice. Hospital Employee or private practice option. Excellent compensation and benefit package. Beautiful setting close to metro areas and the coast. Contact John McCusker, Alpha Physician Search, 800.504.3411 or jmccusker@alphamg.org View additional opportunities at www.alphaps.org

Intensivist

North Shore, Long Island. Excellent opportunity for an Intensivist to join a successful, well-run hospital. Fixed schedule of twelve days per month in this full time position. Competitive salary and full benefits. Shift work available. Easy access to Manhattan, desirable real estate and gorgeous beaches. Contact John Mc Cusker, Alpha Physician Search, 800. 504.3411 or jmccusker@alphamg.org View additional opportunities at www.alphaps.org

Northern California
Hospitalist Opportunity

Sutter Medical Group is seeking a Hospitalist to join their successful expanding Hospitalist program in Auburn, CA. Candidate must have two years of recent experience doing procedures and be able to handle ICU coverage.

- 2-year shareholder track
- Generous compensation
- Competitive benefits package
- Excellent retirement package
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- School system is one of the best in CA
- Great quality of life

Sutter Auburn Faith Hospital, has 95 beds, 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.

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.

Sutter Health
Sacramento Sierra Region

Physician Recruitment
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develops@sutterhealth.org
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STERILE TALC POWDER™

TREATMENT FOR MALIGNANT PLEURAL EFFUSION (MPE)

FDA APPROVED

EXCLUSIVE FEATURES:

- Gamma Irradiated
- Single Use, 5 gram Dosage
- Controlled Particle Size
- Packaged Sterile in a 100ml Glass Vial
- Chest tube administration

DESCRIPTION

Sterile Talc Powder is a sclerosing agent intended for intrapleural administration supplied in a single use 100 ml brown glass bottle, sealed with a gray, 20 mm stopper and covered with a flip-off seal. Each bottle contains a minimum of 5.0 g of Talc USP (Ultra 2000 Talc), either white or off-white to light gray, asbestos-free and brucite-free grade of talc of controlled particle size. The composition of the talc is ³ 95% talc as hydrated magnesium silicate. The empirical formula of talc is Mg3 Si4 010 (OH)2 with a 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 finished product has been sterilized by gamma irradiation.

CLINICAL PHARMACOLOGY

Mechanism of Action

The therapeutic action of talc instilled into the pleural cavity is believed to result from induction of an inflammatory reaction. This reaction promotes adherence of the visceral and parietal pleura, obliterating the pleural space and preventing reaccumulation of pleural fluid.

The extent of systemic absorption of talc after intrapleural administration has not been adequately studied. Systemic exposure could be affected by the integrity of the pleural surface, and therefore could be increased if talc is administered immediately following lung resection or biopsy.

INDICATIONS AND USAGE

Sterile Talc Powder, administered intrapleurally via chest tube, is indicated as a sclerosing agent to decrease the recurrence of malignant pleural effusions in symptomatic patients.

CONTRAINDICATIONS

None known

WARNINGS

None

PRECAUTIONS

1. Future procedures: The possibility of the future diagnostic and therapeutic procedures involving the hemithorax to be treated must be considered prior to administering Sterile Talc Powder. 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 alone for potentially curable malignancies where systemic therapy would be more appropriate, e.g., a malignant effusion secondary to a potentially curable lymphoma.

3. Pulmonary complications: Acute Pneumonitis and Acute Respiratory Distress Syndrome (ARDS) have been reported in association with intrapleural talc administration. Three of the case reports of ARDS have occurred after treatment with a relatively large talc dose (10 g) administered via intrapleural chest tube instillation. One patient died one month post treatment and two patients recovered without further sequelae.

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 tested in cultures of rat pleural mesothelial cells (RPMC) as unscheduled DNA synthesis (UDS) and sister chromatid exchanges (SCEs). None of the talc samples (which were asbestos-free) induced enhancement of 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 a human dose on mg/m2 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 the benefit outweighs the risk.

Pediatric Use: The safety and efficacy of Sterile Talc Powder in pediatric patients have not been established.

Geriatric use: The estimated mean and median ages of patients treated with talc slurry from clinical studies (single-arm or randomized) were 60 and 62 years, respectively. No analyses to specifically evaluate the safety and efficacy in the geriatric population have been reported.

ADVERSE REACTIONS

Intrathoracic administration of talc slurry has been described in medical literature reports involving more that 2000 patients. 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 often reported adverse experiences to intrapleurally-administered talc were fever and pain.

Infection: Complications reported include empyema.

Respiratory: Complications reported include hypoxemia, dyspnea, unilateral pulmonary edema, pneumonia, ARDS, brochopleural fistula, hemoptysis and pulmonary emboli.

Cardiovascular: Complications reported included tachycardia, myocardial infarction, hypotension, hypovolemia and asystolic arrest.

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

Chronic Toxicity: Since patients in clinical studies had a limited life expectancy, data on chronic toxicity are limited.

OVERDOSAGE

No definite relationship between dose and toxicity has been established. Excessive talc may be partially removed with saline lavage.

DOSAGE AND ADMINISTRATION

Sterile Talc Powder should be administered after adequate drainage of the effusion. The success of the pleurodesis appears to be related to the completeness of the drainage of the pleural fluid, as well as the full re-expansion of the lung, both of which will promote symphysis of the pleural surfaces.

The recommended dose is 5 g, dispersed in 50 - 100 ml Sodium Chloride Injection, USP. Although the optimal dose for effective pleurodesis is unknown, 5 g was the dose most frequently reported in the published literature.

Talc Preparation

Prepare the talc slurry using aseptic technique in an appropriate laminar flow hood. Remove talc container from packaging. Remove protective flip-off seal.

Each brown bottle contains 5 g of Sterilized Talc Powder. To dispense the contents:

1. Using a 16 gauge needle attached to a 60-ml LuerLok syringe, measure and draw up 50 ml of Sodium Chloride Injection, USP. Vent the talc bottle using a needle. Slowing inject the 50 ml of Sodium Chloride Injection, USP into the bottle. For doses more than 5 g, repeat this procedure with a second bottle.
2. Swirl the bottle(s) to disperse the talc powder and continue swirling to avoid settling of the talc in the slurry. Each bottle will contain 5 g Sterile Talc Powder dispersed in 50 ml of Sodium Chloride Injection, USP.
3. Divide the content of each bottle into two 60 ml irrigation syringes by withdrawing 25 ml of the slurry into each syringe with continuous swirling. QS each syringe with Sodium Chloride Injection, USP to a total volume of 50 ml in each syringe. Draw air into each syringe to the 60 ml mark to serve as a headspace for mixing prior to administration.
4. When appropriately labeled, each syringe contains 2.5 g of Sterile Talc in 50 ml of Sodium Chloride Injection, USP with an air headspace of 10 ml. Once the slurry has been made, use within 12 hours or discard and prepare fresh slurry. Label the syringes appropriately noting the expiration date and time, with the statement "For Pleurodesis Only – NOT FOR IV ADMINISTRATION," the identity of the patient intended to receive this material and a cautionary statement to SHAKE WELL before use.
5. Prior to administration, completely and continuously agitate the syringes to evenly redisperse the talc and avoid settlement. Immediately prior to administration, vent the 10 ml air headspace from each syringe.
6. Attach the adapter and place a syringe tip on the adapter. Maintain continuous agitation of the syringes.

NOTICE: Shake well before installation. Each 25 ml of prepared slurry in the syringe contains 1.25 g of talc. NOT FOR IV ADMINISTRATION.

Administration

Administer the talc slurry through the chest tube by gently applying pressure to syringe plunger and empty the contents of the syringe into the chest cavity. After application, discard the empty syringe according to general hospital procedures. After the talc slurry has been administered through the chest tube into the pleural cavity, the chest tube may be flushed with 10- 25 ml sodium chloride solution to ensure that the complete dose of talc is delivered.

Following introduction of the talc slurry, the chest drainage tube is clamped, and the patient is asked to move, at 20 to 30 minute intervals, from supine to alternating decubitus positions, so that over a period of about 2 hours the talc is distributed within the chest cavity. Recent evidence suggests that this step may not be necessary.

At the end of this period, the chest drainage tube is unclamped, and the excess saline is removed by the routine continual external suction on the tube.

HOW SUPPLIED

NDC 63256-200-05 Sterile Talc Powder is supplied in a 100 ml brown glass bottle containing 5 g of talc. The sterile bottle is closed with a gray stopper and covered with a flip-off seal.

Storage: Store at Room Temperature (18-25°C). Protect against sunlight.

DISTRIBUTED BY: Bryan Corporation, Woburn, MA 01801

LATEX STERILE R

To place an order or for more information on Product #1680, Sterile Talc Powder™, please contact Bryan Corporation at:

800-343-7711 or visit us at www.bryancorp.com

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