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The updated glycemic control recommendations include targets of 140-180 mg/dL for hospitalized critically ill patients.

Inpatient Glycemic Control Guide Updated

BY MIRIAM E. TUCKER
Elsevier Global Medical News

HOUSTON — New recommendations on inpatient glycemic control issued by the American Association of Clinical Endocrinologists and the American Diabetes Association support less-intensive management goals.

Those revisions sparked a lively and at times heated debate at a special 2-hour evening panel session held during the AACE's annual meeting.

The consensus statement updates more stringent guidelines that were released in 2004. Now, rather than targeting glucose levels of 80-110 mg/dL for hospitalized critically ill patients, targets of 140-180 mg/dL are recommended.

For most noncritically ill hospitalized patients treated with insulin, premeal glucose targets should generally be less than 140 mg/dL and random blood glucose values should be less than 180 mg/dL. (The 2004 guidelines recommended aiming for a premeal glucose level below 110 mg/dL, with a maximal level of 180 mg/dL.) Consideration should be given to reassessing the insulin regimen if glucose levels fall below 100 mg/dL, while the regimen must be modified if glucose levels fall below 70 mg/dL, the two organizations said in the statement, which also recommends strategies to achieve the targets (Endocr. Pract 2009; 15:1-17 and Diabetes Care 2009; 32:1119-31).

Contrary to widespread belief, the statement was not a rapid response to the recent publication of a large randomized controlled trial that showed an increase in mortality risk associated with intensive control of glycemia targeting blood glucose of 81-108 mg/dL (N. Engl. J. Med. 2009;360:1283-7), said Dr. Etie S. Moghissi, who chaired the 10-member AACE/ADA task force.

"Many people thought this statement was a knee-jerk reaction to the [Normoglycemia in Intensive Care Evaluation and

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Severe Asthma's Impact on Children Changing for Better

Oral steroid use fell over last decade.

BY KERRI WACHTER
Elsevier Global Medical News

WASHINGTON — Pediatric patients with severe asthma are younger, use fewer oral steroids, and take lower doses of inhaled steroids today than they did 10 years ago, based on findings from a single-center study of more than 200 patients.

"The use of highly effective medications, developed over the past decade, appears to have changed the clinical manifestations of severe childhood asthma," Dr. Joseph Spahn said at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

Dr. Spahn and his coinvestigators performed a retrospective study of 65 children (aged 6-18 years) referred to a pediatric day program at National Jewish Health for severe asthma between 2004 and 2007. The results were compared with those for a published study of a cohort of 163 children with severe asthma at the facility from 1993 to 1997. Dr. Spahn is the director of the immunopharmacology laboratory at National Jewish Health in Denver.

"Over a 3-year period, we only accumulated 65 children with severe asthma," he noted. "That doesn't mean that we're going out of business because we're not seeing patients any more. Our floors are filled with little kids with severe eczema and multiple food allergies; they're no longer filled with kids with oral steroid–dependent asthma."

The present cohort was younger (a mean 11 years vs. 14 years). The cohort also had an earlier age of asthma onset (a mean 3 years vs. 10 years), and had lower percentiles for height (53 vs. 39), weight (71 vs. 68), and BMI (77 vs. 74).

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INSIDE

Nitric Oxide Adds to Asthma Assessment

BY HEIDI SPLETE
Elsevier Global Medical News

WASHINGTON — Measures of exhaled nitric oxide levels may add another dimension to the evaluation of asthma beyond the information available from the Asthma Control Test and spirometry findings, based on data from a study presented at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

Fractional exhaled nitric oxide (FeNO) may be "a surrogate marker for airway inflammation," Dr. Brian C. Schroer of the Cleveland Clinic said in an interview. Neither the Asthma Control Test (ACT) nor spirometry evaluate airway inflammation.

Dr. Schroer and his colleagues reviewed charts from the asthma-related medical visits of 139 adults, all of whom concurrently completed the ACT, FeNO, and spirometry tests. Approximately 66% of the patients were female, and 78% were white. The study excluded smokers and patients with concomitant conditions including

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New Drugs Alter Treatment Trends

Children • *from page 1*

In addition, "we are seeing fewer children who require chronically administered oral steroid therapy," he said. The percentage requiring chronic oral steroid therapy dropped from 51% in the historic cohort to 28% in the most recent cohort. The duration of oral steroid use also fell from 34 months to 18 months, and the average inhaled steroid dose dropped, from 1,691 mcg to 764 mcg.

There is "an obvious and very distinct difference in the types of inhaled steroids that we use today compared to more than a decade ago," said Dr. Spahn. Children in the current cohort are on second-generation steroids or beclomethasone .

In the latest cohort, 77% were on a leukotriene receptor antagonist, 66% were on a combination inhaled-steroid/long-acting beta-agonist. None of the historic cohort received those medications. The present cohort had higher measures of forced expiratory volume in 1 second (84% vs. 76% of predicted), required less albuterol (34 vs. 72 inhalations per week), and had fewer intubations in the past (13% vs. 21%). The present cohort also had fewer steroid-induced adverse effects.

Dr. Spahn reported that he has received honoraria from both GlaxoSmithKline and Merck & Co. He has also received research support from GSK, Merck, and AstraZeneca Pharmaceuticals LP. ■

Treatment-Related Adverse Effects

	Current rate	Historical rate
Cataracts*	0%	21%
Cortisol suppression (<5 mcg/dL)	51%	56%
Cushingoid stigmata*	2%	75%
Intubation	13%	21%
Myopathy/myalgia*	36%	51%
Osteopenia	51%	46%
Osteoporosis	18%	18%
Vocal cord dysfunction*	31%	14%

*Statistically significant difference.
Source: Dr. Spahn

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Treatment Trends for Severe Asthma

	Current rate	Historical rate
Albuterol* (puffs/week)	34	72
Leukotriene-modifying agent	77%	0%
Fluticasone/salmeterol*	66%	0%
Budesonide*	16%	2%
Fluticasone*	16%	1%
Omalizumab	9%	0%
Tiotropium	8%	0%
Theophylline	8%	n/a
Mometasone*	3%	0%
Beclomethasone HFA*	3%	0%
Flunisolide*	0%	35%
Triamcinolone*	0%	33%
Beclomethasone CFC*	0%	15%

*Statistically significant difference.
Source: Dr. Spahn

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Dr. Burt Lesnick, FCCP, comments: *Better controller therapies for asthma are making a difference. Challenges persist in getting these drugs regularly into the lungs of those who might benefit. Is severe pediatric asthma becoming more a psychosocial problem than a biological one?*

FeNO Sheds Light on Inflammation

Asthma • *from page 1*

chronic obstructive pulmonary disease, cystic fibrosis, and hypereosinophilic syndrome.

Overall, the average FeNO score was 30.8 parts per billion (ppb), the average ACT score was 19.2, the average forced expiratory volume in one second (FEV_1) score was 86.5%, and the average FEV_1/forced vital capacity (FVC) score was 87.4%. Scatter plots showed no correlation between FeNO and either ACT or spirometry measures.

Dr. Schroer said that he was initially surprised by the finding that inflammation was not increased in patients whose ACT scores were either decreased or normal. But the ACT doesn't take airway inflammation into account, and spirometry measures only airway hyperresponsiveness, he said, "So it doesn't surprise me in the long run that the airway inflammation isn't correlated with these other measurements of asthma control."

The lack of correlation held true when the patients were divided into four groups based on asthma severity.

The FeNO measures in patients with intermittent asthma, mild persistent asthma, moderate persistent asthma, and severe persistent asthma were 20.4 ppb, 29.3 ppb, 25.9 ppb, and 39.7 ppb, respectively. The ACT scores in these groups were 22.2, 20.0, 19.7, and 17.1, respectively. The FEV_1 scores were 103%, 95.1%, 90.4%, and 70.4%, respectively, and the FEV_1/FVC scores were 93.3%, 90.7%, 91.2%, and 79.0%, respectively.

The study was supported by the William O. Wagner, M.D., Research and Education Fund. Dr. Schroer had no financial conflicts to disclose.

To view a video interview of Dr. Schroer, go to www.youtube.com/watch?v=1kfS5govgqU&feature=channel_page. ■

Dr. Philip Marcus, MPH, FCCP, comments: *Asthma is a symptomatic condition, and one of our goals is reduction of symptoms. This would be assessed with the ACT. Spirometry generally correlates with symptoms and is best used to assess severity in absolute terms and control. Neither one of these measures assesses inflammation, and at the present time, the measure of exhaled NO (FeNO) provides the best assessment.*

Should this be incorporated into routine asthma assessments? Perhaps in patients with persistent symptoms and/or persistent evidence of ongoing airflow obstruction despite apparent effective therapy.

IN THIS ISSUE

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CHEST PHYSICIAN

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SERIOUS INFECTION

SERIOUS RESULTS

ZYVOX—proven efficacy in nosocomial pneumonia, including those due to MRSA[1-3]*

www.zyvox.com

ZYVOX is indicated in the treatment of nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains) or *Streptococcus pneumoniae* (including multidrug-resistant strains [MDRSP]). MDRSP refers to isolates resistant to 2 or more of the following antibiotics: penicillin, second-generation cephalosporins, macrolides, tetracycline, and trimethoprim/sulfamethoxazole.

ZYVOX should not be used in patients taking any medicinal product which inhibits monoamine oxidases A or B (e.g. phenelzine, isocarboxazid) or within 2 weeks of taking any such medicinal product.

Unless patients are monitored for potential increases in blood pressure, ZYVOX should not be administered to patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis and/or patients taking any of the following types of medications: directly and indirectly acting sympathomimetic agents (e.g. pseudoephedrine), vasopressive agents (e.g. epinephrine, norepinephrine), and dopaminergic agents (e.g. dopamine, dobutamine).

Unless patients are carefully observed for signs and/or symptoms of serotonin syndrome, ZYVOX should not be administered to patients with carcinoid syndrome and/or patients taking any of the following medications: serotonin reuptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), meperidine, or buspirone.

Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported in patients receiving ZYVOX. In cases where the outcome is known, when ZYVOX was discontinued, the affected hematologic parameters have risen toward pretreatment levels. Complete blood counts should be monitored weekly in patients who receive ZYVOX, particularly in those who receive ZYVOX for longer than 2 weeks, those with preexisting myelosuppression, those receiving concomitant drugs that produce bone marrow suppression, or those with a chronic infection who have received previous or concomitant antibiotic therapy. Discontinuation of therapy with ZYVOX should be considered in patients who develop or have worsening myelosuppression.

ZYVOX is not approved and should not be used for the treatment of patients with catheter-related bloodstream infections or catheter-site infections.

ZYVOX has no clinical activity against Gram-negative pathogens and is not indicated for the treatment of Gram-negative infections. It is critical that specific Gram-negative therapy be initiated immediately if a concomitant Gram-negative pathogen is documented or suspected.

Lactic acidosis has been reported with the use of ZYVOX. In reported cases, patients experienced repeated episodes of nausea and vomiting. Patients who develop recurrent nausea or vomiting, unexplained acidosis, or a low bicarbonate level while receiving ZYVOX should receive immediate medical evaluation.

Spontaneous reports of serotonin syndrome associated with the coadministration of ZYVOX and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported. Where administration of ZYVOX and concomitant serotonergic agents is clinically appropriate, patients should be closely observed for signs and symptoms of serotonin syndrome such as cognitive dysfunction, hyperpyrexia, hyperreflexia, and incoordination. If signs or symptoms occur, physicians should consider discontinuation of either one or both agents.

Peripheral and optic neuropathy have been reported in patients treated with ZYVOX, primarily those patients treated for longer than the maximum recommended duration of 28 days. If patients experience symptoms of visual impairment, such as changes in visual acuity, changes in color vision, blurred vision, or visual field defect, prompt ophthalmic evaluation is recommended. Visual function should be monitored in all patients taking ZYVOX for extended periods (≥3 months) and in all patients reporting new visual symptoms regardless of length of therapy with ZYVOX. If peripheral or optic neuropathy occurs, the continued use of ZYVOX in these patients should be weighed against the potential risks.

Convulsions have been reported in patients when treated with ZYVOX. In some of these cases, a history of seizures or risk factors for seizures was reported.

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

The most commonly reported adverse events in adults across clinical trials were nausea, headache, and diarrhea.

IV/Oral

ZYVOX®

(linezolid)

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*Methicillin-resistant *Staphylococcus aureus*.

References: 1. Rubinstein E, Cammarata SK, Oliphant TH, Wunderink RG, and the Linezolid Nosocomial Pneumonia Study Group. Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: a randomized, double-blind, multicenter study. *Clin Infect Dis*. 2001;32:402-412. **2.** Wunderink RG, Cammarata SK, Oliphant TH, Kollef MH, for the Linezolid Nosocomial Pneumonia Study Group. Continuation of a randomized, double-blind, multicenter study of linezolid versus vancomycin in the treatment of patients with nosocomial pneumonia. *Clin Ther*. 2003;25:980-992. **3.** Wunderink RG, Rello J, Cammarata SK, Croos-Dabrera RV, Kollef MH. Linezolid vs vancomycin: analysis of two double-blind studies of patients with methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia. *Chest*. 2003;124:1789-1797.

Please see brief summary of prescribing information on adjacent page.

ZYVOX® linezolid injection, tablets and for oral suspension Brief summary of prescribing information.

INDICATIONS AND USAGE ZYVOX formulations are indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms (**see PRECAUTIONS, Pediatric Use**). **Vancomycin-Resistant *Enterococcus faecium* infections**, including cases with concurrent bacteremia. **Nosocomial pneumonia** caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), or *Streptococcus pneumoniae* (including multidrug-resistant strains [MDRSP*]). **Complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis**, caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*. ZYVOX has not been studied in the treatment of decubitus ulcers. **Uncomplicated skin and skin structure infections** caused by *Staphylococcus aureus* (methicillin-susceptible only) or *Streptococcus pyogenes*. **Community-acquired pneumonia** caused by *Streptococcus pneumoniae* (including multidrug-resistant strains [MDRSP*]), including cases with concurrent bacteremia, or *Staphylococcus aureus* (methicillin-susceptible strains only). To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZYVOX and other antibacterial drugs, ZYVOX should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy. **CONTRAINDICATIONS** ZYVOX formulations are contraindicated for use in patients who have known hypersensitivity to linezolid or any of the other product components. ZYVOX should not be used in patients taking any medicinal product which inhibits monoamine oxidases A or B (e.g. phenelzine, isocarboxazid) or within 2 weeks of taking any such medicinal product. Unless patients are monitored for potential increases in blood pressure, ZYVOX should not be administered to patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis and/or patients taking any of the following types of medications: directly and indirectly acting sympathomimetic agents (e.g. pseudoephedrine), vasopressive agents (e.g. epinephrine, norepinephrine), and dopaminergic agents (e.g. dopamine, dobutamine). Unless patients are carefully observed for signs and/or symptoms of serotonin syndrome, ZYVOX should not be administered to patients with carcinoid syndrome and/or patients taking any of the following medications: serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), meperidine, or buspirone. **WARNINGS** **Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported in patients receiving ZYVOX. In cases where the outcome is known, when ZYVOX was discontinued, the affected hematologic parameters have risen toward pretreatment levels. Complete blood counts should be monitored weekly in patients who receive ZYVOX, particularly in those who receive ZYVOX for longer than two weeks, those with pre-existing myelosuppression, those receiving concomitant drugs that produce bone marrow suppression, or those with a chronic infection who have received previous or concomitant antibiotic therapy. Discontinuation of therapy with ZYVOX should be considered in patients who develop or have worsening myelosuppression.** In adult and juvenile dogs and rats, myelosuppression, reduced extramedullary hematopoiesis in spleen and liver, and lymphoid depletion of thymus, lymph nodes, and spleen were observed. **Mortality Imbalance in an Investigational Study in Patients With Catheter-related Bloodstream Infections, Including Those With Catheter-site Infections**. ZYVOX is not approved and should not be used for the treatment of patients with catheter-related bloodstream infections or catheter-site infections. In an open-label investigational study in seriously ill patients with intravascular catheter-related infections, an imbalance in mortality was seen in patients treated with ZYVOX compared with vancomycin/dicloxacillin/oxacillin. While causality has not been established, mortality was higher in patients treated with ZYVOX who were infected with Gram-negative organisms alone, with both Gram-positive and Gram-negative organisms, or who had no infection when they entered the study. Patients with Gram-positive infections had no difference in mortality. ZYVOX has no clinical activity against Gram-negative pathogens and is not indicated for the treatment of Gram-negative infections. It is critical that specific Gram-negative therapy be initiated immediately if a concomitant Gram-negative pathogen is documented or suspected. *Clostridium difficile*–associated diarrhea (CDAD) has been reported with the use of nearly all antibacterial agents, including ZYVOX, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C difficile*. *C difficile* produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing strains of *C difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur more than 2 months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C difficile*, and surgical evaluation should be instituted as clinically indicated. **PRECAUTIONS** **General Lactic acidosis has been reported with the use of ZYVOX. In reported cases, patients experienced repeated episodes of nausea and vomiting. Patients who develop recurrent nausea or vomiting, unexplained acidosis, or a low bicarbonate level while receiving ZYVOX should receive immediate medical evaluation. Spontaneous reports of serotonin syndrome associated with the co-administration of ZYVOX and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported (see PRECAUTIONS, Drug Interactions). Where administration of ZYVOX and concomitant serotonergic agents is clinically appropriate, patients should be closely observed for signs and symptoms of serotonin syndrome such as cognitive dysfunction, hyperpyrexia, hyperreflexia and incoordination. If signs or symptoms occur physicians should consider discontinuation of either one or both agents. If the concomitant serotonergic agent is withdrawn, discontinuation symptoms can be observed (see package insert of the specified agent(s) for a description of the associated discontinuation symptoms).** Peripheral and optic neuropathy have been reported in patients treated with ZYVOX, primarily those patients treated for longer than the maximum recommended duration of 28 days. In cases of optic neuropathy that progressed to loss of vision, patients were treated for extended periods beyond the maximum recommended duration. Visual blurring has been reported in some patients treated with ZYVOX for less than 28 days. If patients experience symptoms of visual impairment, such as changes in visual acuity, changes in color vision, blurred vision, or visual field defect, prompt ophthalmic evaluation is recommended. **Visual function should be monitored in all patients taking ZYVOX for extended periods (≥3 months) and in all patients reporting new visual symptoms regardless of length of therapy with ZYVOX.** If peripheral or optic neuropathy occurs, the continued use of ZYVOX in these patients should be weighed against the potential risks. Convulsions have been reported in patients treated with ZYVOX. In some of these cases, a history of seizures or risk factors for seizures was reported. The use of antibiotics may promote the overgrowth of nonsusceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken. ZYVOX has not been studied in patients with uncontrolled hypertension, pheochromocytoma, carcinoid syndrome, or untreated hyperthyroidism. The safety and efficacy of ZYVOX formulations given for longer than 28 days have not been evaluated in controlled clinical trials. Prescribing ZYVOX in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. **Information for Patients** Patients should be advised that: ZYVOX may be taken with or without food. They should inform their physician if they have a history of hypertension. Large quantities of foods or beverages with high tyramine content should be avoided while taking ZYVOX. Quantities of tyramine consumed should be less than 100 mg per meal. Foods high in tyramine content include those that may have undergone protein changes by aging, fermentation, pickling, or smoking to improve flavor, such as aged cheeses (0 to 15 mg tyramine per ounce); fermented or air-dried meats (0.1 to 8 mg tyramine per ounce); sauerkraut (8 mg tyramine per 8 ounces); soy sauce (5 mg tyramine per 1 teaspoon); tap beers (4 mg tyramine per 12 ounces); red wines (0 to 6 mg tyramine per 8 ounces). The tyramine content of any protein-rich food may be increased if stored for long periods or improperly refrigerated. They should inform their physician if taking medications containing pseudoephedrine HCl or phenylpropanolamine HCl, such as cold remedies and decongestants. They should inform their physician if taking serotonin re-uptake inhibitors or other antidepressants. *Phenylketonurics:* Each 5 mL of the 100 mg/5 mL ZYVOX for Oral Suspension contains 20 mg phenylalanine. The other ZYVOX formulations do not contain phenylalanine. Contact your physician or pharmacist. They should inform their physician if they experience changes in vision. They should inform their physician if they have a history of seizures. Diarrhea is a common problem caused by antibiotics, which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible. Patients should be counseled that antibacterial drugs including ZYVOX should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When ZYVOX is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by ZYVOX or other antibacterial drugs in the future. **Drug Interactions** ***Monoamine Oxidase Inhibition:*** Linezolid is a reversible, nonselective inhibitor of monoamine oxidase. Therefore, linezolid has the potential for interaction with adrenergic and serotonergic agents. *Adrenergic Agents:* Some individuals receiving ZYVOX may experience a reversible enhancement of the pressor response to indirect-acting sympathomimetic agents, vasopressor or dopaminergic agents. Commonly used drugs such as phenylpropanolamine and pseudoephedrine have been specifically studied. Initial doses of adrenergic agents, such as dopamine or epinephrine, should be reduced and titrated to achieve the desired response. *Serotonergic Agents:* Co-administration of linezolid and serotonergic agents was not associated with serotonin syndrome in Phase 1, 2 or 3 studies. Spontaneous reports of serotonin syndrome associated with co-administration of ZYVOX and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported. Patients who are treated with ZYVOX and concomitant serotonergic agents should be closely observed as described in the PRECAUTIONS, General Section. **Drug-Laboratory Test Interactions** There are no reported drug-laboratory test interactions. **Pregnancy Teratogenic Effects. Pregnancy Category C:** Linezolid was not teratogenic in mice, rats, or rabbits at exposure levels 6.5-fold (in mice), equivalent to (in rats), or 0.5-fold (in rabbits) the expected human exposure level, based on AUCs. However, embryo and fetal toxicities were seen (see **Non-teratogenic Effects**). There are no adequate and well-controlled studies in pregnant women. ZYVOX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Non-teratogenic Effects** In mice, embryo and fetal toxicities were seen only at doses that caused maternal toxicity (clinical signs and reduced body weight gain). A dose of 450 mg/kg/day (6.5-fold the estimated human exposure level based on AUCs) correlated with increased postimplantational embryo death, including total litter loss, decreased fetal body weights, and an increased incidence of costal cartilage fusion. In rats, mild fetal toxicity was observed at 15 and 50 mg/kg/day (exposure levels 0.22-fold to approximately equivalent to the estimated human exposure, respectively based on AUCs). The effects consisted of decreased fetal body weights and reduced ossification of sternebrae, a finding often seen in association with decreased fetal body weights. Slight maternal toxicity, in the form of reduced body weight gain, was seen at 50 mg/kg/day. In rabbits, reduced fetal body weight occured only in the presence of maternal toxicity (clinical signs, reduced body weight gain and food consumption) when administered at a dose of 15 mg/kg/day (0.5-fold the estimated human exposure based on AUCs). When female rats were treated with 50 mg/kg/day (approximately equivalent to the estimated human exposure based on AUCs) of linezolid during pregnancy and lactation, survival of pups was decreased on postnatal days 1 to 4. Male and female pups permitted to mature to reproductive age, when mated, showed an increase in preimplantation loss. **Nursing Mothers** Linezolid and its metabolites are excreted in the milk of lactating rats. Concentrations in milk were similar to those in maternal plasma. It is not known whether linezolid is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZYVOX is administered to a nursing woman. **Pediatric Use** The safety and effectiveness of ZYVOX for the treatment of pediatric patients with the following infections are supported by evidence from adequate and well-controlled studies in adults, pharmacokinetic data in pediatric patients, and additional data from a comparator-controlled study of Gram-positive infections in pediatric patients ranging in age from birth through 11 years (see **INDICATIONS AND USAGE**): nosocomial pneumonia, complicated skin and skin structure infections, community-acquired pneumonia (also supported by evidence from an uncontrolled study in patients ranging in age from 8 months through 12 years), vancomycin-resistant *Enterococcus faecium* infections. The safety and effectiveness of ZYVOX for the treatment of pediatric patients with the following infection have been established in a comparator-controlled study in pediatric patients ranging in age from 5 through 17 years: uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible strains only) or *Streptococcus pyogenes*. Pharmacokinetic information generated in pediatric patients with ventriculoperitoneal shunts showed variable cerebrospinal fluid (CSF) linezolid concentrations following single and multiple dosing of linezolid; therapeutic concentrations were not consistently achieved or maintained in the CSF. Therefore, the use of linezolid for the empiric treatment of pediatric patients with central nervous system infections is not recommended. The C_{max} and the volume of distribution (Vss) of linezolid are similar regardless of age in pediatric patients. However, linezolid clearance is a function of age. Excluding neonates less than a week of age, clearance is most rapid in the youngest age groups ranging from >1 week old to 11 years, resulting in lower single-dose systemic exposure (AUC) and shorter half-life as compared with adults. As age of pediatric patients increases, the clearance of linezolid gradually decreases, and by adolescence, mean clearance values approach those observed for the adult population. There is wider inter-subject variability in linezolid clearance and in systemic drug exposure (AUC) across all pediatric age groups as compared with adults. Similar mean daily AUC values were observed in pediatric patients from birth to 11 years of age dosed q8h relative to adolescents or adults dosed q12h. Therefore, the dosage for pediatric patients up to 11 years of age should be 10 mg/kg q8h. Pediatric patients 12 years and older should receive 600 mg q12h. Recommendations for the dosage regimen for pre-term neonates less than 7 days of age (gestational age less than 34 weeks) are based on pharmacokinetic data from 9 pre-term neonates. Most of these pre-term neonates have lower systemic linezolid clearance values and larger AUC values than many full-term neonates and older infants. Therefore, these pre-term neonates should be initiated with a dosing regimen of 10 mg/kg q12h. Consideration may be given to the use of a 10 mg/kg q8h regimen in neonates with a sub-optimal clinical response. All neonatal patients should receive 10 mg/kg q8h by 7 days of life. In limited clinical experience, 5 out of 6 (83%) pediatric patients with infections due to Gram-positive pathogens with MICs of 4 µg/mL treated with ZYVOX had clinical cures. However, pediatric patients exhibit wider variability in linezolid clearance and systemic exposure (AUC) compared with adults. In pediatric patients with a sub-optimal clinical response, particularly those with pathogens with MIC of 4 µg/mL, lower systemic exposure, site and severity of infection, and the underlying medical condition should be considered when assessing clinical response. **Geriatric Use** Of the 2046 patients treated with ZYVOX in Phase 3 comparator-controlled clinical trials, 589 (29%) were 65 years or older and 253 (12%) were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients. **ADVERSE REACTIONS** **Adult Patients** The safety of ZYVOX formulations was evaluated in 2046 adult patients enrolled in seven Phase 3 comparator-controlled clinical trials, who were treated for up to 28 days. In these studies, 85% of the adverse events reported with ZYVOX were described as mild to moderate in intensity. The incidence (%) of adverse events reported in at least 2% of patients treated with either ZYVOX (n=2046) or all comparators† (n=2001) in these trials were as follows: diarrhea 8.3 and 6.3; headache 6.5 and 5.5; nausea 6.2 and 4.6; vomiting 3.7 and 2.0; insomnia 2.5 and 1.7; constipation 2.2 and 2.1; rash 2.0 and 2.2; dizziness 2.0 and 1.9; and fever 1.6 and 2.1 respectively. The most common adverse events in patients treated with ZYVOX were diarrhea (incidence across studies: 2.8% to 11.0%), headache (incidence across studies: 0.5% to 11.3%), and nausea (incidence across studies: 3.4% to 9.6%). The percent of drug-related adverse events in at least 1% of adult patients in a trial involving the treatment of uncomplicated skin and skin structure infection comparing ZYVOX 400 mg q12h (n=548) to clarithromycin 250 mg q12h (n=537) were 25.4 and 19.6 respectively. The percent of patients discontinuing drug due to drug-related adverse events‡ were 3.5 and 2.4 respectively. The incidence of drug-related adverse events occurring in >1% of adult patients were diarrhea 5.3 and 4.8; nausea 3.5 and 3.5; headache 2.7 and 2.2; taste alteration 1.8 and 2.0; vaginal moniliasis 1.6 and 1.3; fungal infection 1.5 and 0.2; abnormal liver function tests 0.4 and 0.0; vomiting 0.9 and 0.4; tongue discoloration 1.1 and 0.0; dizziness 1.1 and 1.5; and oral moniliasis 0.4 and 0.0 respectively. The percent of drug-related adverse events in at least 1% of adult patients in all other indications of ZYVOX 600 mg q12h (n=1498) versus all other comparators§ (n=1464) with at least 1 drug-related adverse event was 20.4 and 14.3 respectively. The percent of adult patients discontinuing due to drug-related adverse events‡ was 2.1 and 1.7 respectively. The incidence of drug-related adverse events occurring in >1% of adult patients were diarrhea 4.0 and 2.7; nausea 3.3 and 1.8; headache 1.9 and 1.0; taste alteration 0.9 and 0.2; vaginal moniliasis 1.0 and 0.4; fungal infection 0.1 and <0.1; abnormal liver function tests 1.3 and 0.5; vomiting 1.2 and 0.4; tongue discoloration 0.2 and 0.0; dizziness 0.4 and 0.3; and oral moniliasis 1.1 and 0.4. Other adverse events reported in Phase 2 and Phase 3 studies included oral moniliasis, vaginal moniliasis, hypertension, dyspepsia, localized abdominal pain, pruritus, and tongue discoloration. **Pediatric Patients** The safety of ZYVOX formulations was evaluated in 215 pediatric patients ranging in age from birth through 11 years, and in 248 pediatric patients aged 5 through 17 years (146 of these 248 were age 5 through 11 and 102 were age 12 to 17). These patients were enrolled in two Phase 3 comparator-controlled clinical trials and were treated for up to 28 days. In these studies, 83% and 99%, respectively, of the adverse events reported with ZYVOX were described as mild to moderate in intensity. In the study of hospitalized pediatric patients (birth through 11 years) with Gram-positive infections, who were randomized 2 to 1 (linezolid:vancomycin), mortality was 6.0% (13/215) in the linezolid arm and 3.0% (3/101) in the vancomycin arm. However, given the severe underlying illness in the patient population, no causality could be established. The incidence of adverse events reported in ≥2% of pediatric patients treated for uncomplicated skin and skin structure infections‖ with ZYVOX (n=248) or cefadroxil (n= 251) were fever 2.9 and 3.6; diarrhea 7.8 and 8.0; vomiting 2.9 and 6.4; rash 1.6 and 1.2; headache 6.5 and 4.0; upper respiratory infection 3.7 and 5.2; nausea 3.7 and 3.2; trauma 3.3 and 4.8; pharyngitis 2.9 and 1.6; cough 2.4 and 4.0; generalized abdominal pain 2.4 and 2.8; localized abdominal pain 2.4 and 2.8; loose stools 1.6 and 0.8; localized pain 2.0 and 1.6; skin disorder 2.0 and 0.0 respectively. The incidence of adverse events reported in ≥2% of pediatric patients treated for all other indications¶ with either ZYVOX (n=215) or vancomycin (n=101) in comparator-controlled trials were fever 14.1 and 14.1; diarrhea 10.8 and 12.1; vomiting 9.4 and 9.1; sepsis 8.0 and 7.1; rash 7.0 and 15.2; headache 0.9 and 0.0; anemia 5.6 and 7.1; thrombocytopenia 4.7 and 2.0; upper respiratory infection 4.2 and 1.0; nausea 1.9 and 0.0; dyspnea 3.3 and 1.0; reaction at site of injection or of vascular catheter 3.3 and 5.1; trauma 2.8 and 2.0; pharyngitis 0.5 and 1.0; convulsion 2.8 and 2.0; hypokalemia 2.8 and 3.0; pneumonia 2.8 and 2.0; thrombocythemia 2.8 and 2.0; cough 0.9 and 0.0; generalized abdominal pain 0.9 and 2.0; localized abdominal pain 0.5 and 1.0; apnea 2.3 and 2.0; gastrointestinal bleeding 2.3 and 1.0; generalized edema 2.3 and 1.0; loose stools 2.3 and 3.0; localized pain 0.9 and 0.0; and skin disorder 0.9 and 1.0. The percent of pediatric patients treated for uncomplicated skin and skin structure infections‖ with either ZYVOX (n=248) or cefadroxil (n=251) and with ≥1 drug-related adverse event occurring in more than 1% of patients were 19.2 and 14.1 respectively. The percent of pediatric patients discontinuing due to a drug-related adverse event was 1.6 and 2.4 respectively. The incidence of drug-related adverse events reported in more than 1% of pediatric patients (and more than 1 patient) were diarrhea 5.7 and 5.2; nausea 3.3 and 2.0; headache 2.4 and 0.8; loose stools 1.2 and 0.8; vomiting 1.2 and 2.4; generalized abdominal pain 1.6 and 1.2; localized abdominal pain 1.6 and 1.2; eosinophilia 0.4 and 0.4; rash 0.4 and 1.2; vertigo 1.2 and 0.4 and pruritus at non-application site 0.4 and 0.0 respectively. The percent of pediatric patients treated for all other indications¶ with either ZYVOX (n=215) or vancomycin (n=101) and with ≥1 drug-related adverse event occurring in more than 1% of patients were 18.8 and 34.3 respectively. The percent of patients discontinuing due to a drug-related adverse event were 0.9 and 6.1 respectively. The incidence of drug-related adverse events reported in more than 1% of pediatric patients (and more than 1 patient) were diarrhea 3.8 and 6.1; nausea 1.4 and 0.0; loose stools 1.9 and 0.0; thrombocytopenia 1.9 and 0.0; vomiting 1.9 and 1.0; anemia 1.4 and 1.0; eosinophilia 1.4 and 0.0; rash 1.4 and 7.1; oral moniliasis 0.9 and 4.0; fever 0.5 and 3.0; pruritus at non-application site 0.0 and 2.0; and anaphylaxis 0.0 and 10.1# respectively. **Laboratory Changes** ZYVOX has been associated with thrombocytopenia when used in doses up to and including 600 mg every 12 hours for up to 28 days. In Phase 3 comparator-controlled trials, the percentage of adult patients who developed a substantially low platelet count (defined as less than 75% of lower limit of normal and/or baseline) was 2.4% (range among studies: 0.3 to 10.0%) with ZYVOX and 1.5% (range among studies: 0.4 to 7.0%) with a comparator. In a study of hospitalized pediatric patients ranging in age from birth through 11 years, the percentage of patients who developed a substantially low platelet count (defined as less than 75% of lower limit of normal and/or baseline) was 12.9% with ZYVOX and 13.4% with vancomycin. In an outpatient study of pediatric patients aged from 5 through 17 years, the percentage of patients who developed a substantially low platelet count was 0% with ZYVOX and 0.4% with cefadroxil. Thrombocytopenia associated with the use of ZYVOX appears to be dependent on duration of therapy, (generally greater than 2 weeks of treatment). The platelet counts for most patients returned to the normal range/baseline during the follow-up period. No related clinical adverse events were identified in Phase 3 clinical trials in patients developing thrombocytopenia. Bleeding events were identified in thrombocytopenic patients in a compassionate use program for ZYVOX; the role of linezolid in these events cannot be determined (see **WARNINGS**). Changes seen in other laboratory parameters, without regard to drug relationship, revealed no substantial differences between ZYVOX and the comparators. These changes were generally not clinically significant, did not lead to discontinuation of therapy, and were reversible. The percent of adult patients with at least one substantially abnormal hematologic** value in patients treated with ZYVOX 400 mg q12h or clarithromycin 250 mg q12h for uncomplicated skin and skin structure infections were as follows: hemoglobin (g/dL) 0.9 and 0.0; platelet count (x 10^3/mm^3) 0.7 and 0.8; WBC (x 10^3/mm^3) 0.2 and 0.6; neutrophils (x 10^3/mm^3) 0.0 and 0.2 respectively. The percent of adult patients with at least one substantially abnormal hematologic** value in patients treated with ZYVOX 600 mg q12h or a comparator§ were as follows: hemoglobin (g/dL) 7.1 and 6.6; platelet count (x 10^3/mm^3) 3.0 and 1.8; WBC (x 10^3/mm^3) 2.2 and 1.3 and neutrophils (x 10^3/mm^3) 1.1 and 1.2 respectively. The percent of adult patients with at least one substantially abnormal serum chemistry†† value in patients treated with ZYVOX 400 mg q12h or clarithromycin 250 mg q12h for uncomplicated skin and skin structure infections were as follows: AST (U/L) 1.7 and 1.3; ALT (U/L) 1.7 and 1.7; LDH (U/L) 0.2 and 0.2; alkaline phosphatase (U/L) 0.2 and 0.2; lipase (U/L) 2.8 and 2.6; amylase (U/L) 0.2 and 0.2; total bilirubin (mg/dL) 0.2 and 0.0; BUN (mg/dL) 0.2 and 0.0; and creatinine (mg/dL) 0.2 and 0.0 respectively. The percent of adult patients with at least one substantially abnormal serum chemistry†† value in patients treated with ZYVOX 600 mg q12h or a comparator§ were as follows: AST (U/L) 5.0 and 6.8; ALT (U/L) 9.6 and 9.3; LDH (U/L) 1.8 and 1.5; alkaline phosphatase (U/L) 3.5 and 3.1; lipase (U/L) 4.3 and 4.2; amylase (U/L) 2.4 and 2.0; total bilirubin (mg/dL) 0.9 and 1.1; BUN (mg/dL) 2.1 and 1.5; and creatinine (mg/dL) 0.2 and 0.6 respectively. The percent of pediatric patients with at least one substantially abnormal hematologic‡‡ value in patients treated with ZYVOX or cefadroxil for uncomplicated skin and skin structure infections‖ were as follows: hemoglobin (g/dL) 0.0 and 0.0; platelet count (x 10^3/mm^3) 0.0 and 0.4; WBC (x 10^3/mm^3) 0.8 and 0.8; neutrophils (x 10^3/mm^3) 1.2 and 0.8 respectively. The percent of pediatric patients with at least one substantially abnormal hematologic‡‡ value in patients treated with ZYVOX or vancomycin for any other indication¶ were as follows: hemoglobin (g/dL) 15.7 and 12.4; platelet count (x 10^3/mm^3) 12.9 and 13.4; WBC (x 10^3/mm^3) 12.4 and 10.3 and neutrophils (x 10^3/mm^3) 5.9 and 4.3 respectively. The percent of pediatric patients with at least one substantially abnormal serum chemistry^a^ value in patients treated with ZYVOX or cefadroxil for uncomplicated skin and skin structure infections‖ were as follows: ALT (U/L) 0.0 and 0.0; lipase (U/L) 0.4 and 1.2; and creatinine (mg/dL) 0.4 and 0.0 respectively. The percent of pediatric patients with at least one substantially abnormal serum chemistry^a^ value in patients treated with ZYVOX or vancomycin for any other indication¶ were as follows: ALT (U/L) 10.1 and 12.5; amylase (U/L) 0.6 and 1.3; total bilirubin (mg/dL) 6.3 and 5.2; and creatinine (mg/dL) 2.4 and 1.0 respectively. **Postmarketing Experience** Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported during postmarketing use of ZYVOX (see **WARNINGS**). Peripheral neuropathy, and optic neuropathy sometimes progressing to loss of vision, have been reported in patients treated with ZYVOX. Lactic acidosis has been reported with the use of ZYVOX (see **PRECAUTIONS**). Although these reports have primarily been in patients treated for longer than the maximum recommended duration of 28 days, these events have also been reported in patients receiving shorter courses of therapy. Serotonin syndrome has been reported in patients receiving concomitant serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and ZYVOX (see **PRECAUTIONS**). Convulsions have been reported with the use of ZYVOX (see **PRECAUTIONS**). Anaphylaxis, angioedema, and bullous skin disorders such as those described as Stevens Johnson syndrome have been reported. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to ZYVOX, or a combination of these factors. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made and causal relationship cannot be precisely established. **OVERDOSAGE** In the event of overdosage, supportive care is advised, with maintenance of glomerular filtration. Hemodialysis may facilitate more rapid elimination of linezolid. In a Phase 1 clinical trial, approximately 30% of a dose of linezolid was removed during a 3-hour hemodialysis session beginning 3 hours after the dose of linezolid was administered. Data are not available for removal of linezolid with peritoneal dialysis or hemoperfusion. Clinical signs of acute toxicity in animals were decreased activity and ataxia in rats and vomiting and tremors in dogs treated with 3000 mg/kg/day and 2000 mg/kg/day, respectively.

* MDRSP refers to isolates resistant to 2 or more of the following antibiotics: penicillin, second-generation cephalosporins, macrolides, tetracycline, and trimethoprim/sulfamethoxazole.

† Comparators included cefpodoxime proxetil 200 mg PO q12h; ceftriaxone 1 g IV q12h; clarithromycin 250 mg PO q12h; dicloxacillin 500 mg PO q6h; oxacillin 2 g IV q6h; vancomycin 1 g IV q12h.

‡ The most commonly reported drug-related adverse events leading to discontinuation in patients treated with ZYVOX were nausea, headache, diarrhea, and vomiting.

§ Comparators included cefpodoxime proxetil 200 mg PO q12h; ceftriaxone 1 g IV q12h; dicloxacillin 500 mg PO q6h; oxacillin 2 g IV q6h; vancomycin 1 g IV q12h.

‖ Patients 5 through 11 years of age received ZYVOX 10 mg/kg PO q12h or cefadroxil 15 mg/kg PO q12h. Patients 12 years or older received ZYVOX 600 mg PO q12h or cefadroxil 500 mg PO q12h.

¶ Patients from birth through 11 years of age received ZYVOX 10 mg/kg IV/PO q8h or vancomycin 10 to 15 mg/kg IV q6-24h, depending on age and renal clearance.

These reports were of 'red-man syndrome,' which were coded as anaphylaxis.

** <75% (<50% for neutrophils) of Lower Limit of Normal (LLN) for values normal at baseline; <75% (<50% for neutrophils) of LLN and of baseline for values abnormal at baseline.

†† >2 x Upper Limit of Normal (ULN) for values normal at baseline; >2 x ULN and >2 x baseline for values abnormal at baseline.

‡‡ <75% (<50% for neutrophils) of Lower Limit of Normal (LLN) for values normal at baseline; <75% (<50% for neutrophils) of LLN and <75% (<50% for neutrophils, <90% for hemoglobin if baseline <LLN) of baseline for values abnormal at baseline.

^a^ >2 x Upper Limit of Normal (ULN) for values normal at baseline; >2 x ULN and >2 (>1.5 for total bilirubin) x baseline for values abnormal at baseline.

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BMI Affects Asthma Control, Not Treatment Response

BY HEIDI SPLETE
Elsevier Global Medical News

WASHINGTON — Heavier people may have worse asthma control than do their lighter counterparts, but they are not significantly less likely to respond to treatment, based on data from a pair of studies presented at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

In one study of 221 adults with severe asthma, body mass index (BMI) had no significant effect on impaired prednisone absorption or on any abnormalities in prednisone clearance.

Previous studies have shown a relationship between increased weight and asthma severity, said Dr. Joshua Davidson of National Jewish Health in Denver.

To investigate the effects of BMI on the response to steroids for the treatment of asthma, Dr. Davidson and colleagues measured the in vitro glucocorticoid responses to prednisone, dexamethasone, fluticasone propionate, and budesonide in asthma patients in three different weight categories.

A total of 51% of the patients were obese (BMI greater than 30 kg/m^2), 32% were overweight (BMI 25-30), and 17% were normal weight (BMI less than 25).

BMI was positively associated with an increased number of steroid side effects, Dr. Davidson said. But there was no significant association between BMI and forced expiratory volume per second/forced vital capacity (FEV_1/FVC). Also, BMI was not associated with any reduction in prednisone absorption or clearance, or in steroid response, based on two recognized functional measures of steroid response (Imax and IC50).

But asthma control remains a problem for heavier patients. Dr. Hector Ortega of GlaxoSmithKline in Research Triangle Park, N.C., and his colleagues reviewed data from the Asthma Control Characteristics and Prevalence Survey Study (ACCESS), which included 2,238 patients aged 15 years and older from 35 asthma clinics across the United States.

BMI WAS POSITIVELY ASSOCIATED WITH AN INCREASED NUMBER OF STEROID SIDE EFFECTS.

A total of 921 patients met criteria for well-controlled asthma, and 1,317 were not well controlled; 51% of the patients had a BMI of 30 or less, and 49% had a BMI greater than 30. Patients with a history of COPD were excluded from the study.

The researchers found that 65% of the adults with a BMI greater than 30 had poorly controlled asthma, versus 52% of those with a BMI of 30 or less. This difference was statistically significant, Dr. Ortega said.

After controlling for multiple variables, a BMI greater than 30 was independently associated with a 54% increased risk of poorly controlled asthma, he added.

The study was limited by the fact that BMI was divided into only two categories, Dr. Ortega noted. But the results suggest that a high BMI should remain a red flag for clinicians who treat asthma patients, because these patients may need more guidance and supervision to keep their asthma under control, Dr. Ortega said.

Dr. Davidson had no financial conflicts to disclose. Dr. Ortega is employed by GlaxoSmithKline. ■

Dr. Philip Marcus, MPH, FCCP, comments: *For years, we have recognized that obesity adversely affects asthma outcomes. This report helps to understand that the exact relationship between an increase in BMI and poorer asthma control is not based on a particular problem with response to commonly used agents in achieving asthma control. Certainly, our recommendations for obese patients to lose weight should generally improve asthma control as well. We should still be able to treat obese patients with the same medications, but perhaps to expect less.*

Flu Vaccine May Not Be Effective in the Elderly

BY PATRICE WENDLING
Elsevier Global Medical News

CHICAGO — Trivalent inactivated influenza vaccine may not elicit a clinically adequate antibody response in elderly adults, pilot data suggest.

Based on blood assays taken before and 4 weeks after administration of the Fluarix 2007/2008 formula, 88% of 71 community-dwelling older adults, mean age 85 years, failed to mount a fourfold antibody response to any of the three virus strains present in the trivalent influenza vaccine (TIV).

Only two patients had a fourfold antibody response to both influenza A types, H1N1 and H3N2, and none had such a response to all three strains—H1NI, H3N2 and influenza B, Dr. Sean X. Leng said at the annual meeting of the American Geriatrics Society. A fourfold or higher vaccine antibody titer increase, also called positive seroconversion, is the criterion for a clinically adequate antibody response.

In contrast, he noted that the vaccine insert reports that 444 (60%) of 745 persons, aged 18-64 years, had a fourfold antibody response to the H1N1 strain, 461 (62%) had such a response to H3N2, and 575 (77%) did so to the influenza B strain.

"Obviously this is pilot data, but [it does] point out the importance of the need for comprehensive evaluation of this vaccine in older and frail populations," said Dr. Leng of the division of geriatric medicine and gerontology at Johns Hopkins University in Baltimore.

The audience questioned whether immunity would be a more accurate measure of vaccine protection than antibody response in the elderly since they are more likely than the young to have been vaccinated before and thus would have higher baseline antibody levels. Of note, researchers at Stanford University recently reported that even the type of vaccine—TIV or live attenuated influenza vaccine—received in prior years affects both serum antibody and B-cell responses to subsequent vaccination (PLoS ONE 2008;8:e2975).

Most patients in the current study had high baseline titer levels, which would make it more difficult to achieve positive seroconversion, acknowledged Dr. Leng. Patients had received flu vaccine for an average of 7 years prior to study entry, although this was based on self-report and subject to memory bias.

Still, 25 (3.4%) participants reported signs and symptoms of flu-like illness during the 2007-2008 flu season, although laboratory confirmation of a diagnosis of influenza was not performed. No influenza-related deaths were reported.

Influenza is the fourth leading cause of death in older Americans, with the elderly bearing more than 90% of influenza-related mortality.

Dr. Leng noted that those aged 75 years and older make up a small percentage of vaccine trial cohorts, despite being the fastest growing segment of the population. In one vaccine trial, only 11% of patients were at least 75 years old (JAMA 1994;272:1661-5). The one-size-fits-all approach to influenza vaccine needs to be re-examined, as is being done with cancer screening in elderly and other high-risk groups, he suggested.

Patients in the study ranged in age from 72-95 years, 79% were women, and 93% were white. The average number of diagnoses was 3.7 and they included hypertension (67%), osteoarthritis (45%), and dyslipidemia (38%).

Dr. Leng and associates reported no conflicts of interest. The study was sponsored by the National Institute on Aging and the American Federation for Aging Research. ■

Glucose Targets Debated

Updated • *from page 1*

Survival Using Glucose Algorithm Regulation] study. I would like to let you know we started this process last fall," said Dr. Moghissi, of the University of California, Los Angeles.

Indeed, several recent randomized, controlled clinical trials in critically ill patients with diabetes or elevated blood glucose levels have failed to show a significant improvement in mortality with intensive insulin therapy targeting near normal glucose levels. These outcomes have raised concerns that the means for achieving specific glucose targets may play a role in adverse outcomes, particularly with regard to iatrogenic hypoglycemia.

The consensus panel had nearly completed the document just before the NICE-SUGAR study was published, and made only minor modifications to their existing document based on the new study findings. "Our task was really to look at all of the evidence … We needed to come to not only reasonable and achievable, but importantly, very safe targets," Dr. Moghissi said.

Noted Dr. M. Sue Kirkman, vice president of clinical affairs for the ADA, "The emerging evidence from further randomized controlled trials in ICU settings called into question some of the early enthusiasm for intensive treatment targets … But on the other hand, we're also concerned that people might react to these more negative studies by letting the pendulum swing back too far. We really don't want people going back to the bad old days of ignoring hyperglycemia in the hospital, where it's clearly linked to adverse outcomes."

Several audience members expressed that same concern, with some commenting that they had successfully implemented protocols to achieve the lower targets and now wondering whether they were expected to back off. One audience member asked if he would face medicolegal risk if his institution continued to use the lower targets.

Dr. Moghissi replied that hospitals are free to continue as they have been doing but should keep in mind that the current evidence doesn't support it. "These are general recommendations. Nothing is black and white. Medico-legally, you need to do what you think is right for your institution and what is safe."

She added, "I think the targets recommended will be a lot easier to achieve in the majority of community hospitals."

Other speakers reiterated that the data can't be ignored. "I don't know if I'm doing any good with [tight glucose targets], but I know that when other people have tried this in a randomized clinical trial, harm has appeared," said Dr. Framarz Ismail-Beigi, professor of medicine at Case Western University, Cleveland. "And the harm may not be linked to hypoglycemia. I'm not sure that it's even true, but it may be true. We need to determine if it's true."

Dr. Guillermo E. Umpierrez, professor of medicine at Emory University, Atlanta, reminded the audience that benefit from intensive therapy was seen in just one randomized controlled study (N. Engl. J. Med. 2001;345:1359-67). Two other large randomized trials were stopped due to unacceptable rates of hypoglycemia, and now NICE-SUGAR showed evidence of harm.

"The data are clear: If you try to achieve 80-110, you don't gain more, you get more hypoglycemia, and you take the risk of increased mortality," Dr. Umpierrez said.

Dr. Ismail-Beigi and Dr. Kirkman stated that they had no conflicts of interest. Dr. Moghissi, Dr. Hirsch, and Dr. Umpierrez each disclosed financial relationships with several pharmaceutical companies that manufacture diabetes-related products. ■

Summary of Glycemic Control Guidelines

For critically ill patients:

- ▶ Start insulin therapy to treat persistent hyperglycemia, using a threshold of no greater than 180 mg/dL.
- ▶ Once insulin therapy has been started, maintain a glucose range of 140-180 mg/dL.
- ▶ Validated intravenous insulin infusions protocols with demonstrated safety and efficacy, and with low rates of hypoglycemia occurrence, are recommended.
- ▶ With intravenous insulin therapy, frequent glucose monitoring is essential to minimize the occurrence of hypoglycemia and to achieve optimal glucose control.

For noncritically ill patients:

- ▶ For the majority who are treated with insulin, glucose targets should be less than 140 mg/dL premeal and less than 180 mg/dL at random readings, provided these can be safely achieved.
- ▶ More stringent targets may be appropriate in stable patients with previous tight glycemic control.
- ▶ Less stringent targets may be appropriate in terminally ill patients or in those with severe comorbidities.
- ▶ Scheduled subcutaneous administration of insulin, with basal, nutritional, and correction components, is the preferred method for achieving and maintaining glucose control.
- ▶ Prolonged therapy with "sliding scale insulin" as the sole regimen is discouraged.
- ▶ Noninsulin antihyperglycemic agents are not appropriate in most hospitalized patients who require therapy for hyperglycemia.
- ▶ Clinical judgement and ongoing assessment of clinical status must be incorporated into day-to-day decisions regarding treatment of hyperglycemia.

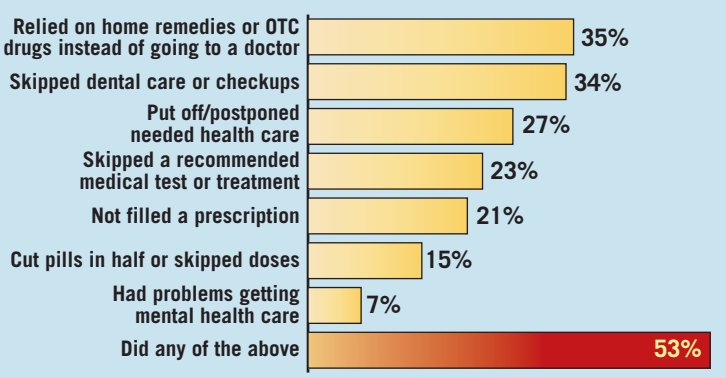
The document also addressed issues regarding safety, cost, and discharge planning, including the following:

- ▶ Overtreatment and undertreatment of hyperglycemia represent major safety concerns.
- ▶ Education of hospital personnel is essential.
- ▶ Caution is required in interpreting the results of point-of-care glucose meters in patients with anemia, polycythemia, hypoperfusion, or use of some medications.
- ▶ Buy-in and financial support from hospital administration are required.
- ▶ Appropriate inpatient management of hyperglycemia is cost effective.
- ▶ Preparation for transition to the outpatient setting should begin at the time of hospital admission, and must involve clear communication with patients and outpatient providers.

DATA WATCH

More Than Half of Americans Skimp on Health Care

In the past 12 months, has a family member in your household done any of the following because of cost?



Note: Based on a survey conducted Feb. 3-12, 2009, among a nationally representative random sample of 1,204 adults.
Source: Kaiser Family Foundation

ELSEVIER GLOBAL MEDICAL NEWS

A REPORT ON THE INFECTIOUS DISEASES SOCIETY OF AMERICA MEETING

Pandemic Flu: Are We Prepared?

BY DR. ROBERT A. BALK, FCCP
Steering Committee Member
ACCP Disaster Response NetWork

Recently, the news headlines were dominated by fear and concern for a possible pandemic of influenza A (H1N1 - swine flu). This scenario is vaguely familiar for those of us over age 40 who remember the mass immunization program in 1976 to prevent a pandemic of swine flu, which fortunately never happened. The good news is that learned people have been discussing and preparing strategies to deal with an inevitable viral pandemic. This effort has learned important information from the past experience with severe acute respiratory syndrome (SARS), HIV, Hanta virus, and multiple drug-resistant tuberculosis. The need for a workable plan has been intensified with recent concerns over the possibility of a pandemic of avian (H5N1) influenza. Given the ease of global travel and the potential for viral reassortment, the question is not if there will be a pandemic, but when and with what virus? Most experts were of the opinion that the next pandemic would involve either seasonal influenza or the more deadly, avian influenza. The current swine flu situation took most experts by surprise.

In an effort to prepare for the eventual pandemic, there has been a yearly conference for the past 4 years designed to address current strategies for preparedness and response to seasonal and pandemic influenza. The Infectious Diseases Society of America (IDSA) has convened this conference for the past 2 years and invited attendees from the World Health Organization (WHO), the Department of Health and Human Services (HHS), the Centers for Disease Control and Prevention (CDC), state and local health officials, policymakers, and other important stakeholders to update the global impact of both seasonal and pandemic influenza, new developments in efficacy and use of vaccines, new treatment strategies for acute infection, and the complexities of the initial and surge response. As a member of the ACCP Disaster Response NetWork, I had the privilege to attend this 2-day conference in Washington, DC, February 2-3, 2009.

In an update on the global impact of avian influenza, Dr. Keiji Fukuda, MPH, of WHO, reported that, at that time, there were over 400 cases of H5N1 (avian influenza) in 15 countries. Despite aggressive treatment and support strategies, the case fatality rate is over 60%, with the majority of deaths resulting from a complicating bacterial pneumonia and/or multiple organ failure. Up to one-third of the cases lack a history of poultry exposure. Of great concern, in addition to the high mortality rate, is the potential of this virus to rapidly mutate and become resistant to available antiviral therapy. Dr. Menno D. de Jong from the University of Amsterdam reported that the current strain of the H5N1 virus is resistant to usual antiviral treatments, a situation that has prompted the investigation of higher-dose therapy and treatment with various combinations of antiviral agents. While we wait for the development of a universal influenza vaccine, the current strategies to address a potential pandemic will rely on stockpiling available antiviral treatment regimens and current vaccines for potential deployment to the regions at risk for the pandemic.

While the plan for stockpiling vaccine and antiviral treatment regimens seems to be reasonable, there were many logistic issues and questions that still need to be answered. Included in these concerns is what to stockpile and where to position these stockpiles to support rapid distribution when necessary. At present, the time necessary to fill vaccine orders is about 20 days, and there must be a method to support rapid engineering of new vaccine as the virus changes. Of course, once a stockpile is established, there will be additional issues with replenishment and how to deal with expiration/replacement of vaccine and antiviral therapy.

Potential Impact of Pandemic Infection

	Moderate Pandemic, 1957	Severe Pandemic, 1918
Illness	9,000,000	90,000,000
Hospitalized	865,000	9,900,000
ICU care	128,750	1,1485,000
Mechanical ventilatory support	64,875	745,000
Deaths	209,000	1,903,000

Centers for Disease Control and Prevention

Treatment discussions focused on some early promising results with combination and high-dose antiviral therapy. The addition of anticytokine therapy or immune-modulating agents still requires additional study before these can be endorsed for inclusion in the management of influenza patients. Dr. John G. Bartlett of the Johns Hopkins University School of Medicine reviewed the bacterial superinfections and other complications seen in influenza patients that are responsible, in large part, for the high mortality rate. He also discussed the need for early identification and administration of appropriate treatment of these superinfections to improve outcome. Prophylactic antibiotic strategies have not been shown to improve outcome.

Dr. Stephen C. Redd, the Director of the Influenza Coordination Unit of the US CDC, emphasized the potential impact of a pandemic infection in the United States (see Table). These numbers bring up concerns of dealing with the surge in hospital beds and resources. There must also be strategies to prevent further spread by imposing certain restrictions on the activities of the population, but there must be allowances to maintain adequate health-care staff and functions necessary to keep society functioning. This latter topic is not typically discussed but has tremendous ramifications in a pandemic, where upwards of 20% of society may be affected by the flu.

In addition to short supplies of food and medical necessities, it was pointed out that there may be shortages of fuel, electricity, and water, if the transportation industry is not able to maintain needed deliveries and/or key workers are not able to report to work. In essence, the question of enough available medical beds for a pandemic may actually take a back seat if there is not any food, water, or electricity to keep the hospital operational.

It is important for experts to critically assess these situations and develop plans to ensure our ability to provide needed care and maintain the health of our societal members during a potential pandemic. We still have a number of issues to resolve and even the potential of an universal vaccine may not be the complete answer. For now, it appears that vaccination is crucial, and early treatment of patients is essential for dealing with a pandemic. We realize the impact is far greater than just the hospital or health-care environment. Fortunately, the current influenza A (H1N1) swine flu does not have the lethality that an H5N1 avian influenza pandemic would have, but it does give us a chance to evaluate our management plans and make needed changes before we are faced with a deadly pandemic. ■

This Month in *CHEST*: Editor's Picks

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

▶ **Assessment of Left Ventricular Function by Intensivists Using Handheld Echocardiography.** *By Dr. R. Melamed, et al.*

▶ **Clara Cell Protein (CC16), a Marker of Lung Epithelial Injury, Is Decreased in Plasma and Pulmonary Edema Fluid From Patients With Acute Lung Injury.** *By Dr. J. A. Kropski, et al.*

▶ **Treatment of Sarcoidosis-Associated Pulmonary Hypertension: A Two-Center Experience.** *By Dr. C. F. Barnett, et al.*

▶ **Accuracy of Whole-Body Plethysmography Requires Biologic Calibration.** *By Dr. P. Poorisrisak, et al.*

CONTEMPORARY REVIEWS IN CRITICAL CARE MEDICINE

▶ **Heparin-Induced Thrombocytopenia: A Contemporary Clinical Approach to Diagnosis and Management.** *By Dr. E. Shantsila, et al.*

CLINICAL COMMENTARY

▶ **Rescue Treatment in Asthma: More Than As-Needed Bronchodilation.** *By Dr. A. Papi, et al.*

ACCP CONSENSUS STATEMENT

▶ **ACCP Consensus Statement on the Respiratory Health Effects of Asbestos: Results of a Delphi Study.** *By Dr. D. E. Banks, FCCP, et al.*

www.chestjournal.org

New at CHEST Online—Social Bookmarking Tools

Social bookmarking is an activity performed over a computer network that allows users to save and categorize personal collections of bookmarks and share them with others. Users may also take bookmarks saved by others and add them to their own collection, as well as subscribe to the lists of others—a personal knowledge management tool (http://en.wikipedia.org/wiki/Social_bookmarking).

Just added to the *CHEST* journal site, at the bottom of each article and in the tool bar of each article are social networking and bookmarking tools.

Now you can store references to *CHEST* articles to sites like Digg, Del.icio.us, Connotia, CiteULike, and others, and you can post links and comments to Facebook and Twitter. ■

Critical Care Commentary

United States Critical Illness and Injury Trials Group

Members of the Organizing and Steering Committees, USCIIT Group
www.usciitg.wustl.edu
Contact USCIITG@wudosis.wustl.edu

The United States Critical Illness and Injury Trials (USCIIT) Group is a new entity, a "network of networks," with the dual missions of fostering investigator-initiated hypothesis testing and strategic planning for clinical research at a national level. Funded by a U13 grant from the National Institute of General Medical Sciences (NIH), the USCIIT Group is establishing an inclusive, multidisciplinary nationwide network of experts in order to promote interactions across established research programs; to improve education and training in the science of clinical trials; and to ensure patient protection and privacy by addressing the ethical, legal, and social implications of critical illness and injury research. The USCIIT Group is led by a steering committee comprising primarily staff from several stakeholder Institutes and Centers at the NIH. Expertise in multidisciplinary clinical research is provided by an Organizing Committee and dozens of USCIIT Group representatives from across the country.

The USCIIT Group differs from other NIH grants that specifically fund studies in that the U13 mechanism creates a "meeting venue" at regular intervals to pursue strategic partnerships, acting as a community "think tank" for clinical research and strategic planning. Given the challenges of scope and geography, the USCIIT Group employs several different means of communication, including triannual face-to-face meetings in the fall, winter, and spring, an e-mail communication network, and an Internet-based information portal (www.usciitg.wustl.edu). The inaugural meeting of the USCIIT Group was held in November 2008 on the Bethesda campus of the NIH (the program is available online at wwwstrategicresults.com/usciitg). At this organizational meeting, over 200 attendees expressed a high level of support for this interdisciplinary, "global" approach to critical illness and injury research. In addition, there was strong interest in creating an interconnected, global network for the conduct of research and the dissemination of new findings. Finally, new synergy was evident as colleagues discovered other investigators with similar research interests possessing different skill sets and perspectives. A number of specific themes emerged, several of which are described briefly below.

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

Fostering Clinical Trials

In response to a summer 2008 USCIIT Group Call for Clinical Projects, 18 investigators presented their clinical hypotheses for testing at a national level. All submitted projects were presented in poster form; several were also selected for podium presentation during plenary sessions. The scientific focus of these clinical projects spanned the time continuum of critical illness and injury, from prehospital settings through full rehabilitation. Moreover, investigators of both children and adults were represented, so that the ontogenic response to critical illness and injury could be studied across all age groups. In an effort to protect the intellectual property of presenters and their audience, all attendees were required to adhere to a written USCIIT Group code-of-conduct, which relies on an implicit pact-based honor system. Specifically, attendees were expected to respect the intellectual property presented and the previous commitments made by presenters and discussants, to disclose competing interests or obligations that may conflict with new or existing clinical projects, and to refrain from using or sharing privileged information. Increased awareness of better endpoints for clinical studies and the ethics of informed consent also were discussed.

We believe that the clinical projects forum will stimulate positive interactions within our critical care community and provide valuable opportunities for researchers to find collaborators for their projects, obtain feedback from national experts, and improve the clinical design of their studies. New investigators will also learn about the science of clinical trials, managing a multidisciplinary team, and preparing grant applications. The 2009 USCIIT Group Call for Clinical Projects will be released this summer; details will be available on the Web site.

Forging a Critical Alliance

The USCIIT Group invited input from several professional organizations, research networks, and federal agencies that advocate for research in the critically ill or injured. Several presenters emphasized that there is substantial existing knowledge, infrastructure, and experience with clinical trials in the United States for the critically ill and injured, both for children and adults. Nevertheless, in light of ongoing, unanswered clinical questions and recent technologic advances, there was consensus that an inclusive, systematic approach to strategic planning in the United States is needed (Cobb et al. *Crit Care Med* 2008; 36:2905). Myriad organizational models were presented, including those used by successful national critical care research organizations in other countries. At this phase in its development, the USCIIT Group has a pressing need to determine how to collaborate efficiently and build teams across existing research networks.

Two NIH programs were discussed that offer significant expertise and resources for the community. The first is the Clinical and Translational Science Awards (CTSA) initiative of the National Center for Research Resources (NIH). CTSA grants are awarded to medical research institutions to improve the performance of research across the nation, reduce the time for translational discoveries to move from bench to bedside, engage all communities in advancing clinical research, and train the next generation of clinical and translational researchers (www.ncrr.nih.gov). The CTSA program currently funds 38 institutions, in effect, creating a national biomedical research network. The CTSA network provides a unique opportunity for critical illness and injury investigators to leverage growing infrastructure to develop novel national clinical research capabilities, education and training for new and established clinical investigators, and the participation of clinicians in community hospitals. The second NIH resource is the Program on Public-Private Partnerships (PPP), the goal of which is to provide advice on the formation of research partnerships that leverage both NIH and non-NIH resources (ppp.od.nih.gov). The PPP Program can help address our community's need for a culture of collaboration and trust that provides mutual benefit. This arrangement can help relieve tensions related to intellectual property concerns, maximizing the ability to answer scientific questions. Practical solutions to decision making were also emphasized.

Core Resources

The need for USCIIT Group core resources was discussed, including expertise in the ethics and conduct of clinical research, biorepositories, and clinical informatics. The ethics of doing research in the special population of the critically ill or injured is particularly challenging, as most of these research subjects, by definition, are not able to provide informed consent. Thus, as noted by Beecher over 30 years ago, true research protection comes from the investigator (Koski. *Am J Respir Crit Care Med* 2004; 169:982). It was agreed that the code-of-conduct reflect the USCIIT Group's first and highest priority of protecting the safety, interests, and well being of research subjects. There was interest in developing a process whereby USCIIT Group investigators receive formal training in clinical research and be certified subsequently by a third party. Finally, broad support was voiced to create an independent USCIIT Group advisory committee to address complex ethical issues.

Multicenter research at a national scale also requires significant investment to optimize the development and maintenance of tissue repositories. A wealth of experience addressing practical considerations for the longevity and quality of de-identified tissue samples has been gained by federal programs sponsored by the Department of Veteran Affairs and by the National Cancer Institute. These include governance, protection of patient privacy, distribution of specimen collection kits, best practices for central vs local tissue processing, logistic support for freezers and alarm systems, Web-accessible inventory logs, and strategic plans for disasters and culling of samples. Genomic repositories are a special case, given the impact of confidentiality on future generations and the ability to store DNA samples for decades.

Finally, there is a growing awareness that critical illness and injury research, because it is conducted typically in the most data-rich environments in medicine, will require substantial new resources to develop more robust clinical information systems and new infrastructure for data sharing. New federal investment in hospital information technology will no doubt help, but real-time capture and analysis of high dimensional data streams (*eg*, heart rate variability) require a level of computational expertise that is not widely available. USCIIT Group investigators agreed that its strategic planning efforts should address both these tissue repository and informatics needs of the community .

In conclusion, the USCIIT Group has established an inclusive, multidisciplinary nationwide, "network of networks" to test hypotheses and improve the robustness of clinical trials. At the inaugural fall meeting, and subsequently tri-annually, the USCIIT Group provides a venue to plan strategically to address the many issues (scientific, ethical, and political) that confound clinical research for the critically ill and injured. The organizational model seeks inclusiveness and encourages participation by all clinicians interested in critical illness and injury, including those who practice in community settings.

The success of the USCIIT Group is based on collaborative leadership, nonhierarchical team culture, and open dialogue that will facilitate communication streams and help link new scientific knowledge with the science of implementation to improve service performance and patient outcomes. ■

The ACCP endorses the USCIIT Group and has sent representatives, including Dr. Curtis Sessler, FCCP; Dr. Neil Halpern, FCCP; Dr. Craig Lilly, FCCP; and Mr. Al Lever, FCCP(Hon), to its meetings.

PRESIDENT'S REPORT

Industry Influence on Continuing Medical Education

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

Over the past 5 years, the print and electronic media has been replete with editorials, and, predominantly negative comments, about perceived conflicts of interest (COI) between industry, physicians, and their professional medical organizations. A vast majority of these communications has not been fair and balanced and attempt to establish misconduct by physicians. I do not agree with these communications that are biased against physicians and industry. The opinions expressed in this article are mine and do not reflect those of the ACCP, its leadership, members, or staff.

Since my early days in practice, my colleagues and I have been living under the suspicion of committing errors, fraud, and abuse. These were the words used by Centers for Medicare and Medicaid Services (CMS) (then HCFA) as they implemented the CPT coding system in the 1980s, followed by strict documentation requirements that misdirected our charting activities from focused information sharing about the patient to documentation for dollars. Our professional organizations are now falling under similar scrutiny by a cadre of individuals who believe we are in collusion with industry to promote industry products and profits.

It is agreed that connections among the pharmaceutical industry, academic physicians, and societies have the potential to affect patient treatment decisions. Industry contributions to medical research, primarily at academic institutions, are approximately three times that of the federal government, and we have all benefited from the results. This investment has yielded insight into disease processes and multiple therapeutic options not available when I completed my medical training. Our patients are living longer, more active lives than they did in 1977. If publication in a peer-reviewed scientific journal is a measure of success, articles resulting from industry-supported research appear twice as often as those from government-funded activities.

It is important to note that the relationships between industry and societies, such as the ACCP, are governed by the Accreditation Council for Continuing Medical Education (ACCME) and the US Food and Drug Administration (FDA). The ACCME examines our conflict of interest policies and their enforcement, while the FDA monitors the activities of industry and can request investigation by the US Department of Justice for suspected health-care fraud. It appears that others believe that this level of oversight is not adequate to prevent inappropriate industry influence. Positions regarding industry-society relationships have been taken by the Institute of Medicine (IOM) and American Association of Medical Colleges (AAMC), as well as self-appointed cadres of individuals intensely concerned that the educational products of our College are being corrupted by industry influence. The ACCME has not been intimidated. After considering feedback to its summer 2008 Calls-for-Comment, the ACCME will not be taking any action to end the commercial support of accredited continuing medical education. Innovations to improve the effectiveness of CME are the primary focus of the ACCME. The ACCME continues to promote its 2006 ACCME Accreditation Criteria and the ACCME Standards for Commercial Support and evaluates CME providers within this framework.

In 2007, the IOM formed the Committee on Conflict of Interest in Medical Research, Education, and Practice to examine conflicts of interest and to recommend steps to manage these conflicts. After extensive review of the situation, the report was released in late April. Anticipating the release of the IOM report, *JAMA* published an "Op Ed" piece in its April 1, 2009, issue.

To quote the authors of the *JAMA* article, "An extensive literature search has documented the influence of gifts on individual physicians." In support of that statement, they cite three articles, none of which would rise to the level of evidence that would include them in an ACCP evidence-based guideline. The AAMC report cited in the references was from a conference that resembled the pseudoscientific conferences held by some of the for-profit medical communications companies.

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Review of the AAMC report leads me to believe that the participants started with the assumption that educators, researchers, and clinicians are easily influenced by any contact with industry.

In my opinion, the important advances made possible by research dollars provided by industry are being overshadowed by some questionable activities generated by their marketing personnel and the for-profit "medical communication" companies hired to develop conferences and literature to advance the use of their products.

If the stringent recommendations of the Op Ed piece were followed, the void created by the withdrawal of our postgraduate programs would rapidly be filled by the for-profit medical education industry. I would much rather acquire my continuing education from the ACCP with its internal controls than the alternative.

It is no secret that we rely on financial support from industry to fulfill our educational mission. The cost to physicians attending our annual meeting is reduced by support from a broad array of research-based pharmaceutical and medical device firms. This support allows us to rent the space where vigorous debate takes place among researchers, academicians, and experienced clinicians. This debate helps shape our clinical approach to disease, as well as the future of medical research.

Without industry support, we would have to increase the registration fee for our annual meeting to between $800 and $1,200, making it prohibitive to many of our colleagues. This would be especially true for recent graduates, many of whom are carrying a significant debt burden. Our popular board review courses would require a similar increase in registration fee.

In response to increasing criticism and scrutiny, The Pharmaceutical Research and Manufacturers of America (PhRMA) has established a set of guidelines, most recently updated in January of this year, which closely describe the rules of engagement between industry and physicians. In addition to compliance with external regulatory bodies, the ACCP has been proactive in establishing firewalls and COI policies. We were in compliance with all of the recommendations contained in the IOM report long before it was made public.

In the current environment, there is a substantial degree of uncertainty within our partners in the research-based industry. It is easier to avoid risk and with the degree of uncertainty generated, many educational programs of other societies have had their funding withdrawn. The College has been fortunate to have a senior staff who have been proactive in engaging our industry partners in a transparent and ethical framework. I believe our relationships remain reasonably intact, although they have required increased time and attention.

While industry is being criticized for its potential influence, most of my clinical colleagues are not entirely naive and are able to apply clinical experience and judgment in their patient care decisions.

I realize that this opinion has been derided in the AAMC publication. Certainly, a degree of skepticism is bred into most experienced physicians who have witnessed many initial research conclusions disproved or modified over the course of time. In the last 2 decades, systems for evaluating and grading the quality of research endeavors have been developed and evidence-based medical practice is evolving.

Unfortunately, these important endeavors are expensive and, in the absence of an increase in government funds, industry support is indispensable.

What is the primary influence industry has on postgraduate medical education? It makes it possible. ■

PCCU

Pulmonary and Critical Care Update

May 2009

▶ **WHO Groups II and III Pulmonary Hypertension: When and How To Treat?**
By Dr. Terence K. Trow, FCCP; Dr. Ray Foley, FCCP; and Dr. James Klinger, FCCP

▶ **An Introduction to Pleural Ultrasonography for the Pulmonary and Critical Care Physician**
By Dr. Paul H. Mayo, FCCP; and Dr. Peter Doelken, FCCP

June 2009

▶ **The Pathophysiology and Treatment of Dyspnea**
By Dr. James Hallenbeck

▶ **Use of the 6-Min Walk Test: A Pro and Con Review**
By Dr. Daniel R. Smith, FCCP

Updates From Recipients of Foundation Awards

Dr. Gregory Efosa Erhabor, FCCP

2008 Humanitarian Project Development Grant Recipient
Project: Asthma Campaign in Ile-Ife
Ile-Ife, Nigeria

Dr. Erhabor founded Asthma and Chest Concerns about 15 years ago, a nongovernmental organization that is based in Ile-Ife, Osun State, Nigeria. His efforts are focused on education through distribution of asthma-related materials, television and radio broadcasts, seminars at both primary and secondary schools, and educational sessions on asthma management with nurses, general practitioners, and physicians.

He notes, "The CHEST Foundation award has contributed immensely to accelerating the work of asthma and chest care education within the Ile-Ife community and the whole of Osun State."

He says that people travel from various cities as far as 300 kilometers to Ile-Ife to participate in the asthma and chest education seminars, which include a comprehensive education on recognizing the symptoms and signs of asthma, prevention of acute asthma attacks, and self-management of asthma. He states, "Notable within the last year, acute emergencies in asthma have been reduced to a bare minimum, and mortality from this disease has not been recorded."

Dr. G. Lakshmipathi, FCCP

2008 Ambassadors Group Humanitarian Recognition Award Recipient
Project: Say "No to Tobacco" Educational Project Addressing School Children
Coimbatore, India

Dr. Lakshmipathi serves as the project creator, director, and member of the team of volunteers, composed of physicians and well-trained individuals, who conduct anti-tobacco educational programs in both the private and public schools in Coimbatore where nearly 20% of children, in the 12- to 18-year age group, smoke or use other tobacco-related products.

Dr. Lakshmipathi notes, "Adequacy of funds (from The CHEST Foundation) has enabled us to spare no time and money to reach, by frequent visits and repeated sessions in small rooms, the poorer corporation schools with less overall facilities. These facilities teach children from poor socioeconomic backgrounds who: (1) have greater exposure to family members using tobacco in every form; (2) are less informed on tobacco hazards; (3) have inadequate parental supervision and guidance; (4) are more vulnerable to tobacco hazards because of poor nutritional status; and (5) are exposed to passive smoking in small, ill-ventilated dwellings."

Dr. Patrick Nana-Sinkam, FCCP

2007 CHEST Foundation and LUNGevity Foundation Clinical Research Award in Lung Cancer Recipient
Project: Circulating miRNA as a Biomarker in Lung Cancer
Ohio State University, Columbus, Ohio

The first aim of Dr. Nana-Sinkam's research was to identify microRNA (miRNA) expression profiles in individuals with lung cancer and matched control subjects to evaluate for the presence of miRNAs. The second aim was to correlate peripheral blood miRNA profiles with primary tumor profiles and histologic diagnosis to determine if miRNA expression in primary lung tumor tissues is reflected by similar expression profiles in peripheral blood and to determine if, following definitive resection of primary lung cancer, miRNA profiles "return to baseline" and can be used as a biomarker for disease. Dr. Nana-Sinkam notes, "In the last year, support from The CHEST Foundation and the LUNGevity Foundation has afforded us the opportunity to conduct allied studies on specific miNAs based on preliminary studies in the peripheral blood. In our initial preliminary data, we identified several miRNAs whose patterns of expression in the peripheral blood mirrored that observed in primary tumors." Dr. Nana-Sinkam will complete his research in July 2009 and submit a final report. ■

CHEST Series Offers Approaches to Pain in ICU

BY JENNIFER STAWARZ
Senior Manager, ACCP Public Relations

Most hospitalized patients experience pain at some point during their stay; however, critically ill patients in the ICU may suffer from pain beyond what is typically seen in a hospitalized patient. Critically ill patients not only experience pain from their life-threatening illness or injury but can have additional pain associated with simple or routine procedures. And, unlike many hospitalized patients, critically ill patients may not be able to communicate that they are in pain or their level of pain. These factors, and more, can make it difficult to recognize and manage pain in the critically ill patient.

Through the Critical Care Institute, the American College of Chest Physicians (ACCP) has spearheaded an initiative that hopes to raise awareness about pain in the ICU and make progress toward eliminating unmanaged pain in the ICU. The ACCP collaborated with the American Association of Critical-Care Nurses and the American Society of Health-System Pharmacists to form a panel of critical care, pain management, and adult education experts to review available pain management literature, assess existing treatment and education strategies, and provide recommendations for future research. As a result of their efforts, the panel developed a five-article series that specifically addresses the current state of pain management in the ICU, as well as barriers to recognizing and treating pain in the critically ill.

As a whole, the article series reviews the complex nature of pain experienced by a critical care patient and details the benefits of taking a comprehensive

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CHEST 2009 in San Diego: Beyond the Beach

San Diego boasts 70 miles of some of the most beautiful beaches in the country. Paired with sunny days and mild temperatures, San Diego is a beachcombers paradise. But, if sun and sand aren't your idea of fun, there are plenty of other ways to enjoy this stunning coastline.

Consider sailing while the sun slinks below the horizon on one of the many charter sailboats around Shelter Island. Find out why San Diego was named No. 1 sport fishing city in America by booking a sport fishing excursion that can take you through the Coronado Islands or even into Baja. Or, try a new sport in the calm waters of Mission Bay on a stand-up paddle board. Glide across the water standing on a huge surfboard, paddle in hand. Lessons are fun and affordable.

CHEST 2009

October 31 - November 5
San Diego, California

For water views and coastal eco-culture, take a trip to Torrey Pines State Reserve, known for rare pines, unique sandstone formations, canopied trails, and million-dollar ocean views. Spanning over 2,000 acres, it preserves the Torrey Pine tree and indigenous wildlife in a natural environment. Or, check out Sunset Cliffs in Ocean Beach. Aptly named, this local gem features 68 acres of bluffs and walking paths that offer panoramic views high above the Pacific Ocean.

Visit www.sandiego.org to find more ways you can enjoy the San Diego coastline while in town for CHEST 2009, October 31 through November 5. Recognized around the world as the authority in clinical chest medicine, CHEST 2009 will offer unique opportunities for clinical education and professional growth. It also marks the start of a year-long celebration of the ACCP's 75th anniversary, so watch for special celebrations and events to be announced.

Early registration fees for CHEST 2009 are in effect now, and ACCP members can save up to $155. Register today at www.chestnet.org. ■

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approach to pain management—one that combines pharmacotherapy with behavioral, social, and communication strategies, interdisciplinary teams, and family involvement.

"The complex nature of caring for the critically ill, particularly in the area of pain management, requires a more holistic approach to patient care," said Dr. Curtis N. Sessler, FCCP, author of an accompanying editorial. "An interdisciplinary critical care team, who uses standard and alternative methods of pain assessment, evaluation, and management, is essential for optimal patient care."

Each article addresses one or more of the pressing issues related to pain management in the ICU, including the challenges of recognizing and evaluating pain, pharmacologic and nonpharmacologic interventions for pain management, palliative care and end-of-life care, and a review of the structured approaches that have been shown to be successful improving pain treatment in the critically ill.

"Although pain in the ICU is inevitable, there is a number of unique interventions that critical care professionals can use to anticipate, manage, and even prevent pain from occurring," said Dr. James A. L. Mathers, Jr., FCCP, President of the ACCP. "Physicians, nurses, pharmacists, and other members of the extended critical care team should continue to make effective pain assessment and management a priority in the ICU."

Starting with the April 2009 issue, the article series is being published in the journal *CHEST* in the "Contemporary Reviews in Critical Care Medicine" section. For more information about the new pain management articles, please visit www.chestjournal.org. ■

Pulmonary Perspectives

Heparin-Induced Thrombocytopenia: A Review

The devastating sequelae of heparin-induced thrombocytopenia (HIT) results from an antibody-mediated adverse reaction to heparin. Paradoxical to the anticoagulant properties of heparin, HIT causes a hypercoagulable state that increases the risk for both venous and arterial thromboses. While only 1 to 3% of patients exposed to heparin develop HIT, the growing use of heparin for treatment and prophylaxis against thromboembolic disease has significantly influenced the prevalence of HIT. With more than 37 million individuals admitted to hospitals on an annual basis in the United States, initiatives to increase the use of thromboprophylaxis to prevent venous thromboembolism in all hospitalized patients will have astounding consequences.

Timely diagnosis and treatment of HIT are aimed at preventing or stabilizing thromboses. However, the clinical diagnosis of HIT remains challenging. The majority of patients who develop thrombocytopenia has multiple potential causes, while thrombosis in those receiving heparin may represent prophylaxis or treatment failure as opposed to HIT. Such clinical ambiguity requires clinicians to carefully assess for HIT, since the mortality rate associated with untreated HIT ranges from 15 to 20%. For these reasons, the American College of Chest Physicians developed guidelines to improve awareness on how to diagnose and treat HIT (Warkentin et al. *Chest* 2008; 133(suppl):340S).

TIMELY DIAGNOSIS AND TREATMENT OF HIT ARE AIMED AT PREVENTING OR STABILIZING THROMBOSES.

Risk Factors for HIT

The occurrence of HIT is highly variable. It is influenced by disease state, type andduration of heparin exposure, and patient gender. Postoperative patients have a higher incidence than medical patients. In particular, the incidence of HIT in orthopedic or cardiac surgery patients ranges between 2% and 4% but is less than 1% in the general medical population. Those receiving unfractionated heparin are more predisposed to developing HIT compared with those who receive low-molecular-weight heparin. Thus, the preponderance of this disease in certain populations may assist in determining aggressiveness to pursue diagnosis and treatment.

Pathophysiology

HIT is an immune-mediated response where the binding of heparin to platelet factor 4 (PF4) results in antibody formation to the PF4/heparin complex. Once produced, HIT antibodies couple with the PF4/heparin complex and activate platelets through their Fc receptors, triggering release of platelet microparticles. Consequent thrombin generation renders the patient in a hypercoagulable state. Uncontrolled, thrombin generation continues to activate platelets, worsening thrombocytopenia, and, potentially, precipitating a vicious cycle of further thrombin formation, which then worsens hypercoagulability. Therefore, expeditious diagnosis and treatment are necessary to halt this process, requiring prevention of further thrombin production to decrease life- and limb-threatening thromboses.

Manifestations of HIT

The majority of patients presents with "typical-onset HIT." This encompasses 70% of cases, with the rest presenting as "rapid-onset HIT" (30%), and an extremely small subset having "delayed-onset HIT." With the exception of delayed-onset HIT, where all patients have a thrombotic event, the incidence of thrombosis is 25 to 70% for HIT. Of those with thrombosis, about 70% are venous (*ie*, deep venous thrombosis, pulmonary embolism, central vein sinus thrombosis), and 30% are arterial (*ie*, limb arterial thrombosis, thrombotic strokes, aortic thrombosis, myocardial infarction).

Patients with "typical-onset HIT" have an unexplained reason for thrombocytopenia that occurs during a specific time period. Initial antibody seroconversion, and, therefore, initial platelet count fall, usually occurs 5 to 10 days after the first heparin dose, which is considered day 0 for heparin exposure. Thereafter, platelet count continues to drop, and the characteristic fall (defined as 30%, 40%, or 50% by various investigators) generally occurs between days 7 and 14. In addition to venous and arterial thromboses, skin lesions at heparin injection sites or an acute systemic (anaphylactoid) reaction may be the primary presenting sign. Indeed, in about 25% of HIT patients, a thrombotic event occurs prior to thrombocytopenia, which further complicates diagnosis.

"Rapid-onset HIT" is caused by administration of heparin to patients who already have circulating HIT antibodies from recent heparin exposure (within the past 100 days). Since antibodies are present at the time of heparin reexposure, significant thrombocytopenia and symptoms occur within 24 h of heparin administration.

"Delayed-onset HIT" is extremely rare. Patients with this type of HIT receive a limited dose of heparin (< 1 day), but all experience a thrombotic event. The mean time to thrombosis after heparin exposure is 9 to 11 days. Excessively high levels of HIT antibody formation activate platelets even in the absence of continuing heparin exposure. Failure to recognize "delayed-onset HIT" is problematic, as resultant reexposure to heparin will propagate thrombosis. Mortality rate can be as high as 25% in this population and requires vigilance for diagnosis.

Diagnosis of HIT

These various manifestations and multiple potential causes for thrombocytopenia complicate the diagnostic picture. HIT is, therefore, considered a clinicopathologic syndrome consisting of three components: (1) heparin exposure; (2) HIT antibody formation; and (3) an unexplained but timely fall in platelet count, whereby some individuals experience a thrombotic event or systemic reaction. Thus, serologic testing for HIT antibodies is essential for diagnosis.

There are two types of assays to determine the presence of HIT antibodies: (1) the platelet activation or "functional" assay (*ie*, serotonin release assay [SRA], heparin-induced platelet activation [HIPA] test) or (2) the PF4-dependent enzyme immunoassay (EIA). Even though these assays are sensitive in detecting HIT antibodies (98%), specificity is quite variable and certainly incomplete for the HIT syndrome. Specificity for the "functional" assays approaches 97% but ranges between 50% and 98% for the EIA. In terms of antibody testing, the "functional" assays are considered the gold standard. Their use is limited, however, since they are labor intensive, time consuming, and expensive.

EIA has rapid turnover but has low specificity. It is more effective in exclusion

Continued on following page

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of HIT than confirmation. The degree of positivity can provide diagnostic information regarding the likelihood of HIT. Expressed as an optical density (OD) value, the greater the magnitude of a positive test result, the greater the probability for HIT. Only 5 to 10% of patients with an OD between 0.4 and 1.0 truly have HIT, while > 90% with an OD > 2.0 have HIT.

Hence, the diagnosis of HIT is difficult and requires the presence of HIT antibodies in the appropriate clinical scenario.

Treatment Options

There are two main goals in the treatment of this prothrombotic condition. First, the immune response propagating the formation of HIT antibodies must be interrupted by the prompt cessation of heparin agents when clinical suspicion for HIT is high. Second, since the time course for thrombosis in HIT is a continuum, thrombin generation must be inhibited to prevent or stabilize thrombotic complications. Failure to do so will result in significant morbidity and mortality.

Currently, there are only four available agents for the treatment of HIT. Of these, three are approved for use in the United States (bivalirudin, lepirudin, argatroban) and one is approved for HIT in Canada, Europe, Australia, New Zealand, Japan, and Korea (danaparoid). The evidence demonstrating the efficacy of these nonheparin agents is imperfect and is derived from prospective, open label, multicenter cohort studies compared with historical controls. Indeed, only one randomized controlled trial (RCT) evaluating HIT treatment exists: open labeled danaparoid vs dextran-70.

Danaparoid is a factor Xa inhibitor. It has a half-life of 19 to 25 h and is renally metabolized. In a small RCT (n=42), the composite endpoint (mortality, thrombosis, and lack of clinical improvement) was significantly lower in the danaparoid group compared with the dextran-treated group, (25.0% vs 58.8%; p = 0.050). There was a trend toward reduced new thrombosis (12.5% vs 41.2%, respectively; p = 0.063). However, danaparoid cross reacts with heparin in approximately 5.3% of patients with HIT.

Bivalirudin is a direct thrombin inhibitor (DTI) with a half-life of 25 to 26 min. Clearance is via the kidneys, and its use is only indicated for patients with HIT in the setting of percutaneous coronary intervention.

Lepirudin is another DTI that is renally eliminated. Serial monitoring of activated partial thromboplastin time (APTT) is required to ensure therapeutic dosing. The half-life of lepirudin is 80 to 102 min and is indicated for patients with HIT. Prospective, open-label cohort studies demonstrate that the development of new thrombotic events is significantly less in those receiving lepirudin compared with historical controls (7.4% vs 25.0%; p < 0.0001). However, mortality did not differ between the two groups.

One must be cautious when prescribing lepirudin to those with a serum creatinine > 90 micromol/L (about 1.0 mg/dL), as these individuals had greater risk of bleeding (about 30% compared with < 5% when serum creatinine < 51 micromol/L (about 0.6 mg/dL) (Lubenow et al. *J Thromb Haemost* 2005; 3:2428).

Additionally, antihirudin antibodies are generated in 30% of patients exposed to lepirudin after the first cycle of treatment and in 70% of patients after the second cycle. Anaphylaxis associated with antihirudin antibodies (as high as 1/625 upon reexposure to lepirudin) has led the European Agency for the Evaluation of Medicinal Products to recommend alternative nonhirudin anticoagulants for HIT in those formerly exposed to lepirudin.

Finally, argatroban is also a DTI where serial monitoring of APTT is required. Elimination is via the hepatobiliary system, with a half-life of 39 to 51 min. New thrombosis formation decreases from 22.4% in historical controls to 8.1% in patients receiving argatroban (p < 0.05). None of the patients died from thrombosis in the argatroban group compared with 4.8% in control subjects (p < 0.05). Dose adjustments must be made for those with hepatobiliary dysfunction (Lewis et al. *Circulation* 2001; 103:1838).

Thus, when clinical suspicion for HIT is high, nonheparin anticoagulants must be provided to decrease morbidity and mortality. In order to impede thrombosis, these agents should be initiated even before serologic confirmation of HIT antibodies when the pretest probability for HIT is great.

Conclusions

HIT is a clinicopathologic syndrome where heparin administration results in antibody formation and potentiates a hypercoagulable state. Confirmation of heparin antibody generation is necessary for diagnosis. Prompt treatment and diagnosis can significantly reduce the devastating consequences of this disease process. Finally, lower extremity duplex ultrasonography looking for deep vein thrombosis is recommended, given the high incidence of thrombosis. ■

Dr. Chee M. Chan
Division of Pulmonary & Critical Care Medicine
Washington Hospital Center
Washington, DC

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

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two years of dietary administration of bosentan to mice produced an increased incidence of hepatocellular adenomas and carcinomas in males at doses as low as 450 mg/kg/day (about 8 times the maximum recommended human dose [MRHD] of 125 mg b.i.d., on a mg/m^2 basis). In the same study, doses greater than 2000 mg/kg/day (about 32 times the MRHD) were associated with an increased incidence of colon adenomas in both males and females. In rats, dietary administration of bosentan for two years was associated with an increased incidence of brain astrocytomas in males at doses as low as 500 mg/kg/day (about 16 times the MRHD). In a comprehensive battery of in vitro tests (the microbial mutagenesis assay, the unscheduled DNA synthesis assay, the V-79 mammalian cell mutagenesis assay, and human lymphocyte assay) and an in vivo mouse micronucleus assay, there was no evidence for any mutagenic or clastogenic activity of bosentan.

Impairment of Fertility/Testicular Function: The development of testicular tubular atrophy and impaired fertility has been linked with the chronic administration of certain endothelin receptor antagonists in rodents. Treatment with bosentan at oral doses of up to 1500 mg/kg/day (50 times the MRHD on a mg/m^2 basis) or intravenous doses up to 40 mg/kg/day had no effects on sperm count, sperm motility, mating performance or fertility in male and female rats. An increased incidence of testicular tubular atrophy was observed in rats given bosentan orally at doses as low as 125 mg/kg/ day (about 4 times the MRHD and the lowest doses tested) for two years but not at doses as high as 1500 mg/kg/day (about 50 times the MRHD) for 6 months. Effects on sperm count and motility were evaluated only in the much shorter duration fertility studies in which males had been exposed to the drug for 4-6 weeks. An increased incidence of tubular atrophy was not observed in mice treated for 2 years at doses up to 4500 mg/kg/day (about 75 times the MRHD) or in dogs treated up to 12 months at doses up to 500 mg/kg/day (about 50 times the MRHD).

Pregnancy, Teratogenic Effects: Category X (See **CONTRAINDICATIONS).**

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, breastfeeding while taking **TRACLEER®** is not recommended. **Pediatric Use:** Safety and efficacy in pediatric patients have not been established. **Use in Elderly Patients:** Clinical experience with **TRACLEER®** in subjects aged 65 or older has not included a sufficient number of such subjects to identify a difference in response between elderly and younger patients.

ADVERSE REACTIONS: Adverse Events: See **BOX WARNING** for discussion of liver injury and **PRECAUTIONS** for discussion of hemoglobin and hematocrit abnormalities. Safety data on bosentan were obtained from 12 clinical studies (8 placebo-controlled and 4 open-label) in 777 patients with pulmonary arterial hypertension, and other diseases. Doses up to 8 times the currently recommended clinical dose (125 mg b.i.d.) were administered for a variety of durations. The exposure to bosentan in these trials ranged from 1 day to 4.1 years (N = 89 for 1 year; N = 61 for 1.5 years and N = 39 for more than 2 years). Exposure of pulmonary arterial hypertension patients (N = 235) to bosentan ranged from 1 day to 1.7 years (N = 126 more than 6 months and N = 28 more than 12 months). Treatment discontinuations due to adverse events other than those related to pulmonary hypertension during the clinical trials in patients with pulmonary arterial hypertension were more frequent on bosentan (5%; 8/165 patients) than on placebo (3%; 2/80 patients). In this database the only cause of discontinuations >1%, and occurring more often on bosentan was abnormal liver function. The adverse drug reactions that occurred in ≥ 3% of the bosentan-treated patients and were more common on bosentan in placebo-controlled trials in pulmonary arterial hypertension at doses of 125 or 250 mg b.i.d. are shown in Table 1:

Table 1. Adverse events* occurring in ≥ 3% of patients treated with bosentan 125-250 mg b.i.d. and more common on bosentan in placebo-controlled studies in pulmonary arterial hypertension

Adverse Event	Bosentan (N = 165)		Placebo (N = 80)	
	No.	%	No.	%
Headache	36	22%	16	20%
Nasopharyngitis	18	11%	6	8%
Flushing	15	9%	4	5%
Hepatic function abnormal	14	8%	2	3%
Edema, lower limb	13	8%	4	5%
Hypotension	11	7%	3	4%
Palpitations	8	5%	1	1%
Dyspepsia	7	4%	0	0%
Edema	7	4%	2	3%
Fatigue	6	4%	1	1%
Pruritus	6	4%	0	0%

***Note: only AEs with onset from start of treatment to 1 calendar day after end of treatment are included. All reported events (at least 3%) are included except those too general to be informative, and those not reasonably associated with the use of the drug because they were associated with the condition being treated or are very common in the treated population.**

In placebo-controlled studies of bosentan in pulmonary arterial hypertension and for other diseases (primarily chronic heart failure), a total of 677 patients were treated with bosentan at daily doses ranging from 100 mg to 2000 mg and 288 patients were treated with placebo. The duration of treatment ranged from 4 weeks to 6 months. For the adverse drug reactions that occurred in ≥ 3% of bosentan-treated patients, the only ones that occurred more frequently on bosentan than on placebo (≥ 2% difference) were headache (16% vs. 13%), flushing (7% vs. 2%), abnormal hepatic function (6% vs. 2%), leg edema (5% vs. 1%), and anemia (3% vs. 1%).

Post-Marketing Experience: Hypersensitivity, Rash, Thrombocytopenia, Jaundice, Anemia requiring transfusion: There have been several post-marketing reports of angioneurotic edema associated with the use of bosentan. The onset of the reported cases occurred within a range of 8 hours to 21 days after starting therapy. Some patients were treated with an antihistamine and their signs of angioedema resolved without discontinuing **TRACLEER®**. In the post-marketing period, in the setting of close monitoring, rare cases of unexplained hepatic cirrhosis were reported after prolonged (> 12 months) therapy with **TRACLEER®** in patients with multiple co-morbidities and drug therapies. There have also been rare reports of liver failure. The contribution of **TRACLEER®** in these cases could not be excluded (see **BOX WARNING**).

References for previous pages: 1. Data on file, Actelion Pharmaceuticals. **2.** Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med*. 2002;346:896-903. **3.** Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet*. 2001;358:1119-1123.

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ACTELION

NetWorks

Fellows at CHEST 2009, HFA Inhalers, CABG vs PCI

Affiliate

What a Fellow Wants

How do you know what the fellows in your training program want? You ask them. We asked this past year via an online survey. All 140 respondents value their membership in the ACCP. However, only half (48.6%) have made it to an annual CHEST meeting, with limited travel funding (81.8%), a tight work schedule (65.0%), and the need to have research to present (28.5%) being the greatest hurdles. Our fellows are a dynamic group, interested in improving the clinical care and teaching they provide and finding success in academic or private practice careers. At CHEST, they would like to see sessions on many topics, with CT interpretation (87.5% rated this as a 4 or 5 on a 5-point scale) and lung pathology review (100%) among the most strongly requested.

The Affiliate NetWork has heard the fellows and wants them to know that for CHEST 2009 in San Diego …

► At our Affiliate luncheon this year, we are featuring Dr. John Heffner, FCCP, who will discuss the tools needed to be an excellent clinical consultant.

► Our CHEST 2009 sessions include both chest CT and lung pathology interpretation—helpful for board exams preparation and daily practice.

► Finally, new this year will be an AFFILIATE LOUNGE, where fellows can kick back, relax with peers, check e-mail, find out about job opportunities, and meet with ACCP leaders.

LTC William Kelly, MC, USA, FCCP
NetWork Chair

Airways Disorders

Hydrofluoroalkane Albuterol Inhalers (HFA) (Non-CFC Albuterol Inhalers)

While HFA inhalers have been available since 1998, their recent widespread use, as required by law, has created a few issues. The new HFA inhalers deliver the same dosage of medication and have the same rate of side effects; however, if not used properly, patients will not get adequate doses. As with older inhalers, it is the technique, not the type of propellant.

HFA inhalers require a slower inhalation, have a weaker spray, and provide a soft mist. These features may lead patients to think they have not received their medication.

Most require 3 to 4 actuations to prime. This was not so critical with the older CFC inhalers, but, now, each "brand" of inhaler requires a different frequency of priming.

HFA inhaler medications are sticky and can clog the hole, reducing the amount of medication delivered. Cleaning instructions are identical for all. The mouthpiece should be cleaned once weekly by running warm water through the top and bottom for 30 s (remove the metal canister first) and then shaking vigorously to remove excess water, followed by air drying overnight. As with CFC-based inhalers, the metal canisters should never be submerged in water or allowed to get wet.

HFA inhalers cost more, as there are no generic equivalents (expected after 2012). Many of the pharmaceutical companies are offering discounts, coupons, and other financial assistance.

There are other differences among the brands. One has the softest spray. Only one has a dose counter to keep track of how much medication is left. A disadvantage of this product is that it has a much shorter expiration timeframe because it has a higher affinity for moisture, and water vapor can enter the canister, decreasing the efficacy. It expires 60 days from the first use compared to 15 to 24 months for most other brands.

Some HFAs contain a small amount of ethanol, and prescribers should be aware of using these products in those who object to alcohol use. Moreover, use of this inhaler can cause a false alcohol breath test if administered shortly (5 to 10 min) after inhaler use.

Dr. Rubin Cohen, FCCP
Steering Committee Member

Interventional Chest/Diagnostic Procedures

Sitting at the forefront of new technology development, the Interventional Chest/Diagnostic Procedures NetWork is uniquely positioned to offer insight and guidance regarding application and dissemination of novel diagnostics and therapeutics. This collaborative cohort of thoracic surgeons and interventional

Continued on page 18

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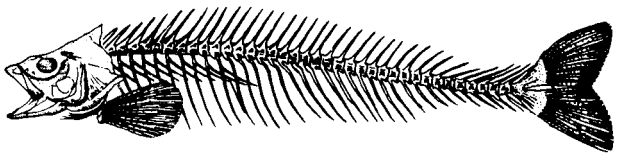

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Continued from page 16

pulmonologists aims to provide experience- and evidence-based information about established and emerging interventional techniques. Several concurrent projects are nearing completion.

The design of an ideal bronchoscopy suite requires an understanding of the specific needs of both interventionists and diagnostic pulmonary physicians. Integration of fluoroscopy, ultrasonography, videobronchoscopy, and specimen preparation areas, as well as ergonomic localization of hardware, needs to be considered. It is hoped that this document will assist individual institutions and health-care provider systems to understand fiscal and physical plant resource needs for such undertakings.

It is becoming increasing apparent that bronchoscopy simulators are important training tools for residents. In a pilot study, residents trained with simulators have an improved grasp of airway anatomy, and, importantly, appear to require far less time "practicing on the patient" to become competent bronchoscopists. We are currently completing data analysis and formalizing recommendations.

Recently, an initiative to formalize guidelines and metrics for interventional bronchoscopy fellowship training has begun. Currently, no such guidelines exist, and attempting to organize and standardize a curriculum is an important mission. There is little doubt that this will be a complex undertaking.

Future projects include defining indications for airway stenting, assessing emerging technologies for bronchoscopic palliation of emphysema, and updating endobronchial ablative therapies for airway obstruction.

Dr. Sudish Murthy, FCCP
NetWork Chair

Members in Industry

The Members in Industry (MII) NetWork was created to foster improved communication between ACCP members in a range of medical industries, such as device and pharmaceutical manufacturers and the general membership of the College. The hope is that this communication will result in improvements in clinical research and medical education that will benefit patients.

This goal has been challenging. Although one-third of the NetWork membership did not come from industry, the NetWork open meeting and the MII-sponsored educational sessions at the annual CHEST meetings attract a disproportionately small number of members from academic or private practice. Without the participation of these members, the communication goal of the NetWork cannot be attained. Therefore, the steering committee has undertaken a series of steps to increase involvement from nonindustry members.

A recent e-mail survey of the MII NetWork membership assessed whether the goals of the NetWork reflected the goals of its members and sought to obtain ideas for future goals. The results of the initial round of this survey indicate that the NetWork must simultaneously orient itself to both industry and nonindustry members and develop sessions at future CHEST meetings to interest more nonindustry attendees.

Based on these findings, the steering committee is pursuing a number of changes. The first would be a potential change in the name of the NetWork from "Members in Industry" to a title more reflective of the wider membership that is desired. Second, NetWork-sponsored sessions at CHEST 2009 will include topics of keen interest to both clinicians and industry.

Longer term goals include bringing one or more nonindustry members onto the NetWork steering committee; and creating a live and Web-based course designed to educate new clinical trialists and update those with prior experience.

Any ACCP member with an interest in learning more about the MII NetWork is encouraged to visit the NetWork Web page at: www.chestnet.org/networks/accp_industry/index.php or to contact the NetWork chair at mforshag@cox.net.

Dr. Mark S. Forshag, FCCP
NetWork Chair

Allied Health

Cross-Cultural Implications in Professional Practice

Medical practices are integrally linked to cultural traditions and, thus, health-care providers and the patient/family members may find conflict in the recommended course of action. Medical professionals need to be made aware of the particular beliefs and practices of Asian-Vietnamese women in order to provide the appropriate level of care that preserves their cultural value and identity and leads to increased survival of both mother and infant. Health belief systems are connected to a culture's values, which can be viewed as feelings and beliefs regarding what is good and bad, desirable and undesirable. In an era of increasing diversity in the health-care environment, several of the health practices that relate to pregnancy, childrearing, and medically related attitudes of women who identify themselves of Vietnamese origin are not at a level of sensitivity that is necessary for health-care providers to deliver the best care possible to this particular subgroup.

We need to develop awareness, sensitivity, and an understanding of these issues as a precursor to serve the medical needs of this community. The development of a cross-cultural competence now allows medical practitioners to feel more confident, especially in issues of nonverbal communication (facial expression, eye movement, and body posture), physical spacing, and communication (translation expressions vs actual words), to handle a more diverse set of health-care beliefs and behaviors. An individual can maintain his/her cultural identity but must adapt within the larger dominant community. Just as one would want to be sensitive (in a multicultural sense), a program needs to reflect on a leadership style (clinical alternatives to care) and the qualities one needs to deal with crisis (acute care emergencies) management and still maintain the particular beliefs of the patient, their family, and spiritual leaders.

Alan Roth, MS, MBA
Steering Committee Member

Cardiovascular Medicine and Surgery

Coronary Artery Bypass Surgery Is Superior to Percutaneous Coronary Interventions in Diabetic and Elderly Patients With Multivessel Disease: Results of a Collaborative Analysis From 10 Randomized Trials

Coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) are two well-established revascularization procedures for patients with coronary disease. Multiple randomized trials and metaanalyses have shown comparable results with these two procedures. Some of the limitations with these trials and metaanalyses include exclusion of patients with more severe coronary disease and reduced left ventricular function and analyses of published aggregate data. To overcome some of these limitations, individual patients' data from 10 randomized trials were pooled for analysis by a group of investigators led by Dr. Hlatky from Stanford University (Hlatky et al. Lancet 2009; 373:1190). The question was "whether the effects of the procedures on mortality are modified by patient characteristics." The 10 trials provided 7,812 patients for this analysis. None of the trials included drug-eluting stents. Thirty-four percent of patients were at least 65 years old. Sixteen percent of patients were diabetics. Median follow-up time was 5.9 years (3 to13 years among the 10 trials).

Overall mortality was 15% in the CABG group vs 16% in the PCI group (p=0.12). The composite outcome of death or repeat revascularization was significantly lower ($p < 0.001$) in CABG patients than the PCI patients, as was the frequency of angina at 1-year, 14% in CABG vs 26% in PCI ($p< 0.0001$).

The mortality in diabetic patients in the CABG group was 23% compared with 29% in PCI patients (p=0.014). This difference persisted, even after exclusion of patients enrolled in the BARI trial.

In patients > 65 years old, CABG mortality was 20% compared to 24% for PCI ($p= 0.002$).

The authors concluded that the pooled data from these randomized trials "provide strong evidence that survival is substantially higher after CABG than PCI in patients with diabetes and multivessel disease." Similarly, older patients have better long-term survival with surgery.

Dr. G. Hossein Almassi, FCCP
Steering Committee Member

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)]*.

ProAir® HFA—the #1 albuterol inhaler[1]

In 2008, there were over 14 million prescriptions for ProAir HFA, more than all other albuterol HFA inhalers combined[1]

ProAir® HFA is indicated in patients 4 years of age and older for the treatment or prevention of bronchospasm with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm.

Important Safety Information

- Inhaled albuterol sulfate can produce paradoxical bronchospasm that may be life-threatening. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister.
- Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma.
- ProAir® HFA, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders (especially coronary insufficiency, cardiac arrhythmias, and hypertension), convulsive disorders, hyperthyroidism, and diabetes.
- Potential drug interactions can occur with beta-blockers, diuretics, digoxin, or monoamine oxidase inhibitors, and tricyclic antidepressants.
- Do not exceed the recommended dose.
- Adverse events, which occurred at an incidence rate of at least 3% with ProAir® HFA, include headache, tachycardia, pain, dizziness, pharyngitis, and rhinitis.

Please see brief summary of Full Prescribing Information on adjacent pages.

TEVA SPECIALTY PHARMACEUTICALS

REFERENCE: 1. IMS Health National Prescription Audit, Total Rx Data, November 2008.

ProAir® HFA
(albuterol sulfate)
Inhalation Aerosol

Fits More Lives