Severe Asthma’s Impact on Children Changing for Better

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 co-investigators 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 161 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 11 years vs. 14 years). The cohort also had an earlier age of asthma onset (a mean 11 years vs. 14 years). The cohort also had an earlier age of asthma onset (a mean 11 years vs. 14 years). The cohort also had an earlier age of asthma onset (a mean 11 years vs. 14 years). The cohort also had an earlier age of asthma onset (a mean 11 years vs. 14 years). The cohort also had an earlier age of asthma onset (a mean 11 years vs. 14 years). The cohort also had an earlier age of asthma onset (a mean 11 years vs. 14 years). The cohort also had an earlier age of asthma onset (a mean 11 years vs. 14 years). The cohort also had an earlier age of asthma onset (a mean 11 years vs. 14 years). The cohort also had an earlier age of asthma onset (a mean 11 years vs. 14 years).

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 re-assessing 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. Ette 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]

Critical Care Institute
American College of Chest Physicians
The U.S. Critical Illness and Injury Trials Group debuts.

See page 8.

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...
New Drugs Alter Treatment Trends

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 91% 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.

“Is there 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 asthma medications 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 (FEV1) 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 L.P.

Dr. Burt Lesnick, M.D., FCCP, Georgia

Dr. Stephen A. Geraci, M.D., FCCP, Mississippi

Dr. Richard Fischel, M.D., FCCP, California

Dr. Doreen Addrizzo-Harris, M.D., FCCP, New York

Dr. Keith M. Wille, M.D., FCCP, Alabama

Researchers have examined FeNO as an additional asthma assessment tool. Studies have shown that FeNO is a good marker of airway inflammation in patients with asthma.

FeNO Shed 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 inhaled steroid score was 19.2, the average forced expiratory volume in one second (FEV1) score was 86.5%, and the average inhaled steroid/long-acting beta agonist score was 46%.

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ZYVOX — proven efficacy in nosocomial pneumonia, including those due to MRSA**

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, dopamine), 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, trycyclic 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 (e.g. 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.

Convolusions 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.

**Metabolite-resistant Staphylococcus aureus.


Please see brief summary of prescribing information on adjacent page.
The effectiveness of the immediate treatment and [2] increase the Bloodshot That bacteria will develop resistance and it is not treatable by BV because of other antibiotics. In general, BV is a NOSOL, non-specifically specific infection of the lamina semiovata. The patient is treated with a broad-spectrum antibiotic that inhibits blood-borne pathogenic bacteria. This is usually effective in treating BV. The patient is monitored for improvement and may be reevaluated in 48 hours or until symptoms resolve.

2. Treatment of BV includes antibiotic therapy, such as oral or topical antibiotics. It is important to follow the recommended duration of treatment, which is typically 7-10 days. The patient may be asked to use a antibiotic or antibiotic cream to help relieve symptoms and prevent reinfection.

3. Follow-up care is important to ensure the patient is responding to treatment and to monitor for any side effects. The patient should be instructed to report any adverse effects to their healthcare provider.

4. To prevent reinfection, the patient should avoid sexual contact during treatment and for 7 days after completing antibiotic treatment.

5. BV is a contagious condition, so it is important to follow proper hygiene practices to prevent the spread of the bacteria. This includes regular hand washing and not sharing personal items such as towels, pillowcases, and underwear.

6. Lifestyle changes, such as maintaining a healthy diet and practicing good hygiene, can help reduce the risk of developing BV in the future.

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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 FluTrends 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 the three strains—H1N1, 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 744 persons, aged 18-64 years, had a fourfold antibody response to the H1N1 strain, 461 (62%) had such a response to H1N2, 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 it 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.
CRITICAL CARE MEDICINE

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 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 their institution should go back on. 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, profes sor 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 involving any good with “tight glucose targets,” 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 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 infusion 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, prandial, and correction components, is the preferred method for achieving and maintaining glucose control.

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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?

Relied on home remedies or OTC drugs instead of going to a doctor 35%
Skipped dental care or checkups 34%
Put off/postponed needed health care 27%
Skipped a recommended medical test or treatment 23%
Not filled a prescription 21%
Cut pills in half or skipped doses 15%
Had problems getting mental health care 7%
Did any of the above 53%

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


Updated from page 1
Recently, the news headlines were dominated by fear and concern for the 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, Ebola 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 global travel and the potential for viral reassembly, 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 discuss 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 greater concern to those of us attending the conference is that 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 viral 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 logistical issues and questions that still need to be answered. Included in these concerns is one-to-one stocking 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.

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 considered 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 morality rate. He also discussed the need for early identification and administration of appropriate treatment of these superinfections. Many of the 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 realize that 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.

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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.
The United States Critical Illness and Injury Trials Group (USCIIT Group) is a new entity, a “network of networks,” with the dual missions of fostering investigator-initiated hypothesis testing and strategic planning for critical care research at a national level. Funded by a U13 grant from the National Institute of General Medical Sciences (NH), 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 two ways. First, 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.uscigng.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 www.strategicresults.com/uscigng). 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 emerged 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.

**Forging a Critical Alliance**

The USCIIT Group invited input from several professional organizations, re-search networks, and federal agencies that advocate for research in the critically ill or injured. Several presenters emphasized that 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.

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 across 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 (NH). CTSA grants are awarded to clinical 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.

The second NIH resource is the Program on Public-Private Partnerships (PPP), the goal of which is to provide opportunities for collaborative research endeavors. 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 Becherer 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 management 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 collections, and storage 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 both appropriate data streams (eg, heart rate variability) require a level of computational expertise that is not currently available. USCIIT Group investigators agreed that strategic planning efforts should address both these tissue repositories 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 found 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, non-hierarchical team culture, and open dialogue that will facilitate communication streams and bridge the gap in scientific knowledge with the science of implementation to improve service performance and patient outcomes.

The ACCEND 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

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 attempts 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 HCPA) 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 IOM report, 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.

Continued on following page
Continued from previous page

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 pharmaceutical and medical device firms.

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.
Dr. Gregory Efosa Erhabor, FCCP
2008 Humanitarian Project Development Grant Recipient
Project: Asthma Campaign in 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 the 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 tumors 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 miRNAs 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.
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 pain experts, 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. In this article series, we will review the complex nature of pain experienced by a critical care patient and details the benefits of taking a comprehensive approach.
S

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 sinks below the horizon on one of the many charters sailing around Shelter Island. Find out why San Diego was named No. 1 fishing city in America by booking a sport fishing excursion that can take you through the Coronado Islands or even out to Baja. Or, try a new 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.

For water views and coastal eco- tours, 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, the Torrey Pine tree and indigenous wildlife in a natural environment. Or, check out Sunset Cliffs in Ocean Beach. Apply 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 - November 5. Recognized around the world as the authority in clinical chest medicine, CHEST 2009 will offer unique opportuni ties 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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to pain management—one that combines pharmacotherapy with behavioral, social, and communication strategies, interdisciplinary teams, and family involvement.

“The complex nature of caring for those critically ill patients 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 care 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 in improving pain management 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 management and assessment 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.
TIMELY DIAGNOSIS AND TREATMENT OF HIT ARE AIMED AT PREVENTING OR STABILIZING THROMBOSSES.

We do our own billing at our practice, and we do quarterly chart audits. When questions arise, we always go to Coding for Chest Medicine. We feel Coding for Chest Medicine is the gold standard of resources for pulmonary and critical care medicine.

—Sandy Kalic, RN, Practice Manager
Eastern Ohio Pulmonary Consultants, Boardman, OH

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 have 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).

Risk Factors for HIT
The occurrence of HIT is highly variable. It is influenced by disease state, type and duration 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, expedient 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 exposure 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
There are two main goals in the treatment of this prothrombotic condition. First, the immune response propagating 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, and 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 hours 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 control 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 more often reacts with heparin antibodies (as high as 1/625 upon reexposure to lepirudin) and in 70% of patients after the second cycle. Finally, argatroban is also a direct thrombin inhibitor (DTI) with a half-life of 23 to 26 minutes. 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 development of testicular tubular atrophy and impaired fertility were evaluated only in the much shorter duration fertility studies in which males had been exposed to bosentan. In the same study, doses greater than 2000 mg/kg/day (about 32 times the MRHD) were associated with mice produced an increased incidence of hepatocellular adenomas and carcinomas in males at doses as low as 500 mg/kg/day (about 8 times the MRHD). In a comparison of fertility in male rats (the critical species) among the compounds in development, all exhibited organ toxicity at the lower limit of exposure, whereas there was no evidence for any metabolic or developmental toxicity of bosentan. Impairment of Fertility/Testicular Function: In a 2-year rat fertility study, doses up to 675 mg/kg/day (about 50 times the MRHD) were associated with an increased incidence of hyperplasia of the adrenal gland in males at doses as high as 5000 mg/kg/day (about 33 times the MRHD). There have been several post-marketing reports of angioneurotic edema associated with the use of bosentan. The adverse drug reactions that occurred in ≥ 3% of bosentan-treated patients, the only ones that occurred more often on bosentan was abnormal liver function. The adverse drug reactions that occurred in ≥ 3% of bosentan-treated patients, the only ones that occurred more often on bosentan was abnormal liver function. 

In conclusion, 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 developing consequences of this disease process. Finally, lower extremity duplex ultrasonography looking for deep vein thrombosis is recommended, given the high incidence of thrombosis.

Table 1. Adverse events occurring in ≥ 3% of patients treated with bosentan (125-250 mg/day) and common in bosentan in placebo controlled studies in pulmonary arterial hypertension.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Bosentan (N = 105)</th>
<th>Placebo (N = 104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>36 (22%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>8 (5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>16 (11%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Flushing</td>
<td>15 (10%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Migraine</td>
<td>14 (9%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (5%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>7 (4%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>7 (4%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6 (4%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>5 (3%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (5%)</td>
<td>4 (4%)</td>
</tr>
</tbody>
</table>

Note: only one drug toxicity was observed in the placebo group in this study. Lepirudin, argatroban, and danaparoid are DTIs. 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 hours 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 control 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 more often reacts with heparin antibodies (as high as 1/625 upon reexposure to lepirudin) and in 70% of patients after the second cycle. 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 minutes.
Fellows at CHEST 2009, HFA Inhalers, CABG vs PCI

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 (65.9%), 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.

Airways Disorders
Hydrofluoroskylene 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. 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.

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 pulmonary vasculitits, including Dr. Rubin Cohen, FCCP, Steering Committee Member.

Continued on page 18
PULMONARY & CRITICAL CARE MEDICINE (PCCM)  SECTION CHIEF VA MEDICAL CENTER  PORTLAND, OREGON

Responsibilities include oversight of clinical, educational and research endeavors, and caring for outpatients and inpatients. A record of academic productivity as a Clinician-Scientist or Clinician-Educator is preferred. Board certification in PCCM is required; training in Sleep Medicine is desirable. Portland VAMC is affiliated with Oregon Health & Science University (OHSU); the successful candidate will be appointed as an Associate or Full Professor, as qualified. This position may require a pre-employment physical and drug test. For job-specific questions, contact Karen Frank, Administrative Manager at 503-220-3413. For application information call 503-273-5236 or visit http://www.portland.med.va.gov/Departments/A&FHR/Staffing/Job_announcements/Title38/T38-09-0087-DG.pdf

Please send application to Human Resources, P.O. Box 1034, Portland, Oregon, 97207. Applicant must be US citizen with current physician licensure and relevant experience. The VA offers competitive salary and benefits packages. A recruitment bonus may be available. EOE

Marietta Pulmonary Medicine  Suburban Atlanta

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

Pulmonary Critical Care Specialist

Northern, New Jersey - Desirable locale within short drive of NYC. Pulmonary Critical Care specialist needed to join a successful single specialty practice. Sleep optional. Partnership in twenty-four months. Fully renovated community hospital on beautiful well-maintained campus. John McCusker, Alpha Physician Search, 800-504-3411 or jmccusker@alphamg.org. View additional opportunities. www.alphamg.org

Pulmonary Disease

Established, busy practice has opportunities available at regional healthcare provider just minutes from large metropolitan area. Applicants must be ABIM BE/BC in internal medicine, pulmonary disease, critical care and sleep disorders medicine. Strong competitive compensation package and benefits. If interested, please mail CV to Boe Mackin, 1850 State Street, New Albany, IN 47150 or call 812-949-5596. Visit our web site at www.floydmemorial.com for more information.

Pulmonary Critical Care Physician

Connecticut – Pulmonary Critical Care Physician needed to join a private practice. Well-maintained facility and hospital. Excellent compensation and benefit package. Option for hospital employee or partnership. Beautiful setting close to metro areas and the coast. Contact John McCusker, Alpha Physician Search, 800-504-3411 or jmccusker@alphamg.org. View additional opportunities. www.alphamg.org

Monarch HealthCare  A MEDICAL GROUP, INC.

Monarch HealthCare is a physician owned company in one of the most desirable areas of the country-Orange County, CA. We are seeking exceptional specialists in the areas of Critical Care and Hospitalist Medicine to join our growing medical group team. Monarch offers a pleasant work environment, a collegial physician group and capable operational staff supported by a strong infrastructure dedicated to excellence in clinical care and service. If you enjoy being part of a dynamic and innovative team, this is your opportunity.

Critical Care Intensivist/Hospitalist Specifics:

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Very competitive wages and benefits including bonus plan, vacation, CME, malpractice, insurance, matched retirement savings and more

Requirements:

- BC/BE Critical Care Medicine
- Authorized to work in the US

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the initial round of this survey indicate the goals of its members and sought to obtain the participation of these members, a portionately small number of members in a range of medical industries, such as device and pharmaceutical manufacture, cannot be attained. Therefore, the steering committee has undertaken a series of activities, including setting up the CHEST meetings to attract a disproportionately large number of participants. This was achieved through the development of a comprehensive group of published aggregate data. The steering committee is pursuing a number of activities, including 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 CHEST 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

Cross-Cultural Implications in Professional Practice

Medical practices are integrally linked to cultural traditions and, thus, healthcare 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 healthcare environment, several of the health practices that relate to pregnancy, childcare, and medically related attitudes of women who identify themselves of Vietnamese origin are not at a level of sensitivity that is necessary for healthcare 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 expressions, 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 the use 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. Mark S. Forshag 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 to 13 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 CABG is superior to PCI in patients who are at least 65 years old.” Further work is needed to determine whether 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

All beta-adrenergic agonists, including albuterol, are known to be substantially excreted by the kidney, and the risk of toxic reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

10 OVERDOSAGE

The expected symptoms with overdose are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats per minute, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia. Hypokalemia may also occur. As with all sympathomimetics, cardiovascular arrest and even death may be associated with the use of PROAIR HFA Inhalation Aerosol.

Treatment consists of discontinuation of PROAIR HFA Inhalation Aerosol together with appropriate symptomatic therapy. The judicious use of a cardiological or other beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdose of PROAIR HFA Inhalation Aerosol.

The oral median lethal dose of albuterol sulfate in mice is greater than 2,000 mg/kg (approximately 6,200 times the maximum recommended daily inhalation dose for adults on a mg/m2 basis and approximately 6,400 times the maximum recommended daily inhalation dose for children on a mg/m2 basis). In mature rats, the subcutaneous median lethal dose of albuterol sulfate is approximately 450 mg/kg (approximately 3,000 times the maximum recommended daily inhalation dose for adults on a mg/m2 basis and approximately 4,000 times the maximum recommended daily inhalation dose for children on a mg/m2 basis). In young rats, the subcutaneous median lethal dose is approximately 3,000 mg/kg (approximately 14,000 times the maximum recommended daily inhalation dose for adults on a mg/m2 basis and approximately 6,400 times the maximum recommended daily inhalation dose for children on a mg/m2 basis). The oral median lethal dose has not been determined in animals.

Mfd by: Teva Specialty Pharmaceuticals LLC
Horsham, PA 19044

Mfd by: IVAX Pharmaceuticals Ireland
Waterford, Ireland

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Manufactured In Ireland

P9A908BS-P

Rev. 09/10

Dr. Sudish Murthy, FCCP
NetWork Chair
1 INSTRUCTIONS AND USAGE

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.

2 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)].

3 WARNINGS & PRECAUTIONS

3.1 Cardiovascular Effects

Beta-agonist use, 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, they 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 QT interval, and ST-segment depression. Therefore, PROAIR HFA Inhalation Aerosol, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially those with congestive heart failure, angina pectoris, or hypertension.

3.2 Pulmonary Effects

The safety and effectiveness of PROAIR HFA Inhalation Aerosol were demonstrated in a 6-week clinical trial in 116 patients 12 years of age and older with asthma comparing doses of 180 mcg four times daily to placebo. Although the adverse event profile and clinical response were similar between the active comparator and PROAIR HFA Inhalation Aerosol, the marketed active comparator HFA-134a inhaler was comparable.

3.3 Use of Anti-inflammatory Agents

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 and may require re-evaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids.

3.4 Cardiovascular Effects

Beta-agonist use, 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, they 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 QT interval, and ST-segment depression. Therefore, PROAIR HFA Inhalation Aerosol, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially those with congestive heart failure, angina pectoris, or hypertension.

3.5 Do Not Exceed Recommended Dose

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with pre-existing cardiovascular disease, even in the absence of known cardiac disease, but cardiac arrest following an unexpected development of a severe acute asthma crisis and subsequent hypoxia is suspected.

4 ADVERSE REACTIONS

4.1 General Information

The adverse reaction information presented in the tables below reflects the data from placebo-controlled clinical trials in which PROAIR HFA Inhalation Aerosol was administered to symptomatic adult and pediatric patients with reversible obstructive airway disease. The safety and effectiveness of PROAIR HFA Inhalation Aerosol are well established in pediatric patients 4 years of age and older.

The adverse events reported with PROAIR HFA Inhalation Aerosol were generally similar to those observed with albuterol sulfate, and were consistent with the known clinical pharmacology of beta-adrenergic agonists. The adverse reactions listed below reflect the data from placebo-controlled clinical trials in which PROAIR HFA Inhalation Aerosol was administered to symptomatic adult and pediatric patients with reversible obstructive airway disease. The incidence of adverse reactions was assessed with the use of PROAIR HFA Inhalation Aerosol (180 mcg albuterol four times daily 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 serum digoxin levels in patients who are receiving albuterol and digoxin concomitantly [see PROAIR HFA Inhalation Aerosol].

4.2 Cardiovascular Effects

May decrease levels of 16% and 22% in serum digoxin levels were demonstrated after single dose intravenous administration of digoxin to patients with normal renal function 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 serum digoxin levels in patients who are receiving albuterol and digoxin concomitantly [see PROAIR HFA Inhalation Aerosol].

4.3 Metabolism and Sedation

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, have been reported in patients exposed to beta-agonists during pregnancy. Of known, caution is advised in the coadministration of beta-agonists with non-potassium sparing diuretics. Consider monitoring potassium levels.

4.4 Local Reactions

In the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may vary depending on the active comparator. The safety and effectiveness of PROAIR HFA Inhalation Aerosol were demonstrated in a 6-week clinical trial in 116 patients 12 years of age and older with asthma comparing doses of 180 mcg four times daily to placebo. Although the adverse event profile and clinical response were similar between the active comparator and PROAIR HFA Inhalation Aerosol, the marketed active comparator HFA-134a inhaler was comparable.

4.5 Other Adverse Reactions

In clinical trials with PROAIR HFA Inhalation Aerosol, adverse events reported with PROAIR HFA Inhalation Aerosol were generally similar to those observed with albuterol sulfate, and were consistent with the known clinical pharmacology of beta-adrenergic agonists.
REFERENCE: 1. IMS Health National Prescription Audit, Total Rx Data, November 2008.

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

± Inhalation of 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.

In 2008, there were over 14 million prescriptions for ProAir HFA, more than all other albuterol HFA inhalers combined¹

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