VOL. 4 • NO. 5 • MAY 2009

CHEST Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

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The use of chlorhexidine-impregnated dressings over insertion sites reduced major catheter-related infections by 60%.

Dressings Cut Catheter-Related ICU Infections

BY MARY ANN MOON
Elsevier Global Medical News

The rate of major catheter-related infections among ICU patients decreased by 60% when dressings impregnated with chlorhexidine gluconate were secured over insertion sites for arterial or central venous catheters, investigators reported.

That decrease was achieved among ICU patients participating in a multicenter study in France, even though the background rate of catheter-related infections already was extremely low, said Dr. Jean-Francois Timsit of University Joseph Fourier, Grenoble, France, and his associates.

They conducted a randomized, controlled trial to assess chlorhexidine-impregnated sponges, because small, unpublished studies of the dressings had yielded promising results. The trial involved 1,636 medical and surgical patients treated in seven ICUs at three university hospitals and two general hospitals. The patients were randomly assigned to receive either chlorhexidine dressings or standard dressings over catheter insertion sites.

Use of the chlorhexidine dressings cut the rate of major catheter-related infections from 1.4/1,000 catheter-days to 0.6/1,000 catheter-days. That protective effect was consistent both for gram-negative and gram-positive organisms, as well as for arterial and central venous catheters, the investigators said (JAMA 2009;301:1231-41).

Skin and catheter cultures showed a significant decrease in bacterial colonization with the chlorhexidine dressings.

The researchers estimated that the number needed to treat to prevent one major infection was 117 catheters.

Eight patients developed contact dermatitis with the chlorhexidine dressings, which resolved when the dressings were removed. All eight patients had multiple organ failures, subcutaneous edema, and fragile skin.

Dr. Timsit and his colleagues also studied whether decreasing

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Study: PPI Was No Help for Poorly Controlled Asthma

Results cast doubt on impact of reflux.

BY ROBERT FINN
Elsevier Global Medical News

Aggressive control of gastroesophageal reflux does not appear to improve asthma symptoms, a study has shown.

The findings challenge the theory that people with poorly controlled asthma frequently have reflux, and that treatment would lead to better asthma control.

The multicenter, double-blind, randomized controlled trial involved 412 adults whose symptoms of asthma were inadequately controlled despite the use of moderate to high doses of inhaled corticosteroids. Participants were assigned to receive either a placebo or 40 mg of esomeprazole, a prescription proton pump inhibitor, twice daily for 24 weeks. This dose was higher than that typically used to treat symptomatic gastroesophageal reflux (N. Engl. J. Med. 2009; 360:1487-99).

The study was conducted by the research group of the American Lung Association Asthma Clinical Research Centers, and the article was prepared by a writing committee led by Dr. John G. Mastronarde of Ohio State University Medical College, Columbus.

Although only 15% of the participants reported a history of gastroesophageal reflux, ambulatory pH monitoring revealed that 41% of patients in the placebo group and 40% in the esomeprazole group had evidence of reflux. This is a common finding among patients with asthma—for many, their reflux is asymptomatic.

Patients kept daily diaries of their asthma symptoms, and they were assessed by

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INSIDE

NCCN Updates Lung Cancer Guidelines

BY DAMIAN McNAMARA
Elsevier Global Medical News

HOLLYWOOD, FLA. — Updates to the National Comprehensive Cancer Network's clinical guidelines add regimens containing cetuximab or pemetrexed to first-line treatment options for recurrent or metastatic non–small cell lung cancer.

A cetuximab (Erbitux), vinorelbine (Navelbine), and cisplatin regimen is now an option for patients who have a performance status of 0-1 and meet criteria for use of cetuximab. Another choice combines cisplatin and pemetrexed (Alimta) for this same group of patients.

For patients with a performance status of 2, the NCCN also added the option of cetuximab, vinorelbine, and cisplatin, again with the proviso that the patient meet cetuximab criteria, including EGFR (epidermal growth factor receptor) expression by immunohistochemistry.

"Best supportive care or palliative care is still recommended

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ICU Infections

Dressings • *from page 1*

the number of dressing changes (following the first such change at 24 hours after catheter insertion) would affect infection outcomes. The group assigned to a delayed dressing change every 7 days showed a rate of catheter-related infection similar to the rate of the group assigned to standard dressing changes every 3 days.

That suggests that it is safe to delay dressing changes in order to minimize occasions for potential catheter contamination, they added

The study results "have the potential to change the standard of care for insertion and maintenance of intravascular catheters," noted Dr. Eli N. Perencevich of the University of Maryland, Baltimore, and Dr. Didier Pittet of the University of Geneva Hospitals and the WHO Alliance for Patient Safety, in an editorial comment that accompanied the report.

The "relatively simple" use of a chlorhexidine-impregnated dressing may decrease further the already low rates of infection achieved through optimal ICU practices, they said (JAMA 2009;301:1285-7). ■

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Panel Revises Cancer Guidelines

Lung Cancer • *from page 1*

for performance status 3-4 patients," Dr. David S. Ettinger, FCCP, said in a presentation of the updated guidelines at the annual conference of the NCCN.

Pemetrexed maintenance therapy also was added as an option until progression for patients with nonsquamous histology who experience tumor response or stable disease after two cycles of first-line chemotherapy.

This was a category 2B recommendation, however, indicating that the 30 physicians on the guidelines panel were not in complete agreement.

Pemetrexed won Food and Drug Administration approval in September 2008 for use in combination with cisplatin as a first-line therapy for locally advanced or metastatic nonsquamous non–small cell lung cancer. It is not indicated in squamous cell lung cancer.

Cetuximab is not FDA approved in NSCLC. When defining criteria for cetuximab use, the NCCN cited the abstract for the phase III FLEX (Cisplatin/Vinorelbine +/– Cetuximab as First-Line Treatment of Advanced Non–Small Cell Lung Cancer) study, which showed a small survival benefit in combination with cisplatin and vinorelbine; it was presented during the 2008 annual meeting of the American Society of Clinical Oncology.

"What takes precedence over any of these guidelines is participation in a clinical trial," said Dr. Ettinger, professor of oncology at Johns Hopkins University in Baltimore.

The panel removed three adjuvant chemotherapy regimens that were previously recommended for patients who had comorbidities or were unable to tolerate cisplatin. The duos of gemcitabine (Gemzar) plus carboplatin; docetaxel (Taxotere) plus carboplatin; and gemcitabine plus docetaxel are no longer recommended.

The guideline panel also added information to systemic therapy recommendations for advanced or metastatic disease, including first-, second-, and third-line strategies. This "clarifies some of the combinations we would use," Dr. Ettinger said.

One new clarification states that a third cytotoxic drug in first-line therapy for advanced or metastatic disease does not increase survival, with the exception of bevacizumab (Avastin) and cetuximab in treatment-naive patients who have a performance status of 0-1.

THE NCCN STILL DOES NOT RECOMMEND ROUTINE SCREENING WITH CT. 'AVAILABLE DATA ARE CONFLICTING; THUS, CONCLUSIVE DATA ... ARE NECESSARY.'

Erlotinib (Tarceva) also is a first-line option +/– chemotherapy for patients who have an EGFR mutation or gene amplification, or who have never smoked. This is a category B recommendation, however, and the update now states that therapy other than erlotinib should be considered for any patient with a KRAS gene mutation.

Docetaxel, pemetrexed, and erlotinib are second-line therapy recommendations. "If you are using pemetrexed first line, your only choices would be docetaxel and erlotinib," Dr. Ettinger said.

For systemic therapy for advanced or metastatic disease, the guidelines recommend only erlotinib as third-line therapy because it has proven survival that is superior to best supportive care. Investigational agents are not recommended as third-line therapies, Dr. Ettinger said.

Principles of radiation therapy for patients with NSCLC also were revised and updated.

The NCCN still does not recommend routine screening with CT. "Available data are conflicting; thus, conclusive data from ongoing national trials are necessary to define the benefits and risks associated with screening for lung cancer with low-dose CT," a new entry in the guidelines explains.

Recommendations for a PET scan were changed to recommend a PET/CT scan. "Addition of CT adds about 10%-15% specificity. You really get better resolution and correlation with PET/CT," said Dr. Ettinger,

Some specific pretreatment recommendations by cancer stage are new since the guidelines were last updated in February 2008. For example, mediastinotomy and CT-guided fine-needle aspiration are new options to evaluate the pathology of mediastinal lymph nodes with stage IIIA disease. In addition, endobronchial ultrasound biopsy is a new option for pretreatment evaluation of stage IIIB disease (T1-T4 N2-N3).

Also, the guidelines now differentiate adjuvant therapy for patients with T1-T2 N2 mediastinal lymph node–positive findings according to whether disease is local or systemic.

Dr. Ettinger is a consultant for AstraZeneca Pharmaceuticals LP, BioNumerik Pharmaceuticals Inc., Bristol-Myers Squibb Co., Eli Lilly & Co., Genentech Inc., GlaxoSmithKline, ImClone Systems Inc., Merck & Co., Novartis, Pfizer Inc., Sanofi-Aventis, and Travanti Pharma Inc. He receives grant support from Genentech, Pharmion Corp., and Novartis. He is a scientific advisor for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Genentech, GlaxoSmithKline, ImClone, Merck, Novartis, and Pfizer. ■

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CHEST PHYSICIAN (ISSN 1558-6200) is published monthly for the American College of Chest Physicians by Elsevier Inc., 60 B Columbia Rd., 2nd flr., Morristown, NJ 07960, 973-290-8200, fax 973-290-8250.

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Moxifloxacin Improved TB Triple-Drug Therapy

BY MIRIAM E. TUCKER
Elsevier Global Medical News

Moxifloxacin increased the proportion of tuberculosis cultures converting to negative at 8 weeks by nearly 20% when added to the usual first-line triple-drug treatment regimen in a single-center, phase II trial in Brazil.

Compared with control patients who received ethambutol, more patients who received moxifloxacin were culture negative after just 1 week of treatment. While the findings don't prove that moxifloxacin can shorten overall TB treatment times, "our data add to a growing body of evidence that suggests that moxifloxacin could shorten tuberculosis treatment by initially eradicating a greater number of organisms and improving the sterilizing activity of combination drug regimens," Dr. Marcus B. Conde and his associates wrote in the Lancet (2009; 373:1183-9).

At baseline, the study's 146 patients were all sputum smear–positive for *Mycobacterium tuberculosis* that was not resistant to isoniazid, rifampicin, or ethambutol. They received recommended doses of isoniazid, rifampicin, and pyrazinamide by directly observed treatment and were randomized to receive also either 400 mg moxifloxacin with an ethambutol placebo or 15-20 mg/kg ethambutol plus moxifloxacin placebo.

Negative sputum cultures were achieved at week 8 by 59 of the 74 patients in the moxifloxacin group (79.7%), compared with 45 of 72 with ethambutol (62.5%), a difference of 17.2%. Among only the subjects who had sputum culture data at 8 weeks, those proportions were 59 of 64 with moxifloxacin (92.1%), versus 45 of 61 controls (73.7%), for a difference of 18.4%. (All missing data were deemed as treatment failures in the intent-to-treat analysis.)

'MOXIFLOXACIN COULD SHORTEN TUBERCULOSIS TREATMENT BY INITIALLY ERADICATING A GREATER NUMBER OF ORGANISMS.'

After 1 week, 9 of 69 in the moxifloxacin group (13%) had negative sputum cultures, compared with 2 of the 68 ethambutol subjects (3%), said Dr. Conde of Federal University of Rio de Janeiro and his associates, who included researchers from his own institution and from the Johns Hopkins University, Baltimore. At every week after enrollment, patients assigned to moxifloxacin had a higher rate of culture conversion than did those assigned to ethambutol, and the differences were significant at every time point except for weeks 6 and 7. The median time to consistently negative cultures was 35.0 days in the treatment group, compared with 48.5 days for the control group.

Adverse events did not differ by treatment group. There were eight serious events in each group, in a total of 12 patients. Only one event, a grade 3 cutaneous reaction, was deemed to be related to the study drug—and that was to ethambutol, not moxifloxacin. Only five patients discontinued treatment because of toxic effects, and no clinically or statistically significant changes in the QTc interval were recorded in patients in either group.

Seven patients had recurrence of TB—three in the moxifloxacin group at 11, 16, and 27 months after completing treatment, and four in the ethambutol group at 6, 7, 22, and 32 months. Six of the seven isolates were tested for drug resistance, and all remained susceptible to isoniazid and rifampicin, Dr. Conde and his associates wrote.

No drug previously has been shown to substantially enhance the activity of the isoniazid/rifampicin/pyrazinamide combination, noted Dr. Hans L. Rieder in an accompanying editorial.

"The trial's finding that culture conversion to negative occurred in 80% of patients in the moxifloxacin group, compared with 63% in the control group is, therefore, surprisingly large," said Dr. Rieder of the tuberculosis department, International Union Against Tuberculosis and Lung Disease, Kirchlindach, Switzerland.

Fourth-generation fluoroquinolones appear to have similar bactericidal activity to isoniazid—and possibly better sterilizing capability. Thus, moxifloxacin might even improve the efficacy of triple therapy for TB that is multiresistant (resistant to isoniazid plus rifampicin), Dr. Rieder added, as long as it isn't extensively drug resistant.

The study was funded by the U.S. Food and Drug Administration Office of Orphan Product Development, with additional support from the U.S. National Institutes of Health. All of the authors declared that they have no conflicts of interest. ■

Mannitol Challenge Tested Asthma Quickly

BY HEIDI SPLETE
Elsevier Global Medical News

WASHINGTON — A mannitol challenge test was safe, easy to perform, and took significantly less time than a methacholine test did when used to evaluate adult asthma patients, based on data from a study of 49 patients with well-controlled asthma.

Methacholine tests often are used to measure airway hyperresponsiveness, but these tests are time consuming and resource intensive, said Dr. Jennifer P. DeMore of the department of medicine at the University of Wisconsin, Madison.

"Mannitol is an indirect challenge that may reflect the level of inflammation currently in the airway," Dr. DeMore said.

To compare the effectiveness and tolerability of methacholine versus mannitol in evaluating airway response, Dr. DeMore and her colleagues evaluated a subset of patients enrolled in the Best Adjustment Strategy for Asthma in the Long Term (BASALT) study, an ongoing research project being conducted by the Asthma Clinical Research Network. The average age of the patients was 34 years, and all were taking inhaled corticosteroids daily. Subjects were excluded if they were pregnant or had acute respiratory illness within 4 weeks of the study.

The findings were presented at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

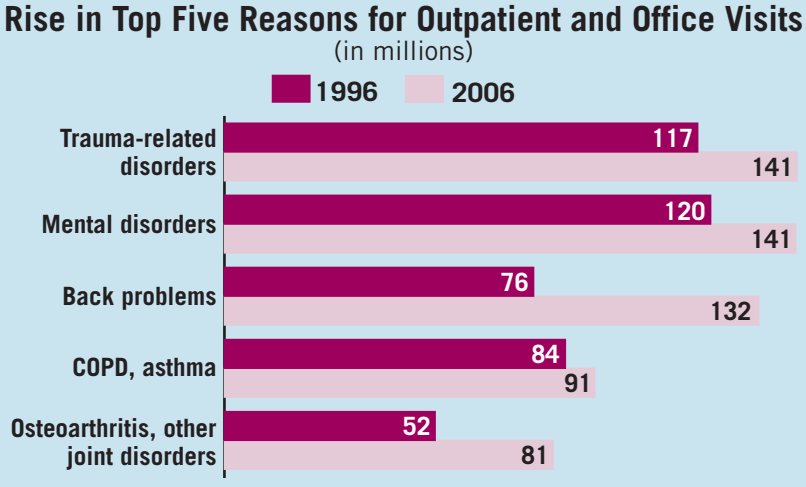
Overall, the mannitol challenge test took an average of 27 minutes, versus 56 minutes for a methacholine test, a significant time savings. Two patients were excluded because of a ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) of less than 70%. Of the remaining 47 patients, 47% achieved 15th percentile density (PD_{15}) with a median dose of 315 mg mannitol. By comparison, 89% achieved a provocative methacholine concentration (PC_{20}) with a median methacholine concentration of 2.5 mg/mL. The median FEV_1 decrease was 17% for mannitol and 22% for methacholine, and the correlation coefficient between mannitol and methacholine was 0.37.

Each participant underwent a mannitol challenge 1 week after undergoing a methacholine challenge. The mannitol was loaded into an inhaler, and no specialized equipment was required.

There was a variance in procedure time for both tests among different centers participating in the study, which suggests a learning curve, Dr. DeMore noted. But the mannitol was safe and well tolerated as part of a larger asthma trial, and the results suggest that it may be a useful option for clinicians once they learn the technique. As part of a larger study, "we hope to contrast mannitol vs. methacholine to characterize asthma phenotypes and predict responses to corticosteroids," Dr. DeMore said.

Dr. DeMore had no financial conflicts to disclose. ■

DATA WATCH



Note: Based on Medical Expenditure Panel Survey data for visits to hospital outpatient departments and office-based providers.
Source: Agency for Healthcare Research and Quality

Elsevier Global Medical News

Asthma Study

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spirometry every 4 weeks. Depending on the definition of poor asthma control, between 42% and 61% of all participants experienced at least one episode, and 18% required an urgent-care visit or a course of prednisone.

There were no significant differences in any of those measures between patients taking placebo and those taking esomeprazole.

There were no significant differences between the groups in any of the secondary outcomes, including several measures of pulmonary function, asthma symptoms, asthma control, and quality of life.

The study was supported by grants from the National Heart, Lung, and Blood Institute and the American Lung Association. Esomeprazole and placebo were supplied by AstraZeneca, which manufactures esomeprazole under the brand name Nexium.

Several members of the writing committee disclosed receiving consulting or lecture fees from AstraZeneca, and they also reported relationships with several other pharmaceutical companies including GlaxoSmith-Kline, Genentech, Boehringer Ingelheim, Cornerstone Therapeutics, Novartis, Sepracor, MedImmune, Schering-Plough, and Forest. ■

Adult Asthma Patients Lack Treatment Knowledge

BY DENISE NAPOLI
Elsevier Global Medical News

WASHINGTON — Nearly half (42%) of adult asthma patients incorrectly believed they could stop taking their controller medications when their symptoms subside, according to a recent survey.

Furthermore, even though 94% of patients indicated that they understood the difference between controller medications and quick-relief medications, 69% also believed that quick-relief medications could be taken on a daily basis.

The findings, from the General Awareness and Perceptions II (GAP II) survey, were presented in a poster at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

According to the authors, led by Dr. Reynold A. Panettieri of the University of Pennsylvania, Philadelphia, the survey results underscore a need for more asthma education among physicians and patients.

"It is never appropriate to stop or taper controlled asthma medication," he said in an interview. "Asthma is a chronic disease that requires long-term control even when symptoms are not present."

A total of 1,001 adult patients and 300 primary care physicians completed the survey between June 27 and August 18, 2008. Among the physicians, 41% indicated that they treated 15 or more asthma patients per week, and 26% indicated that they had been in practice for more than 20 years. Among patients, the mean age was 47 years, slightly more than one-third had completed college or graduate study, and 62% used controller medications. A total of 59% used rescue medications.

The survey also revealed that 55% of patients believed their asthma was well controlled if they logged just one emergency department visit per year, and 56% believed that their asthma could qualify as well controlled even with two urgent doctor visits per year.

"If patients have a positive experience at their doctor appointments, are encouraged to ask questions and are well informed, they'll be more likely to remain compliant with their medication," Dr. Panettieri said.

The study was a follow-up to GAP I, conducted in 2007, whose results are available at www.asthmagap.com. The current study was conducted under the auspices of the Asthma and Allergy Foundation of America with support from AstraZeneca. ■

Medicaid Status Linked To Uncontrolled Asthma

BY KERRI WACHTER
Elsevier Global Medical News

WASHINGTON — Medicaid insurance, low levels of education, and recent cold/flu or sinus infection were linked to an increased risk of uncontrolled asthma in a study of almost 2,000 adult primary care patients.

Patients with less than a high school education were four times as likely to have uncontrolled asthma (adjusted odds ratio 4.09) as those with more education, Richard H. Stanford, Pharm.D., reported at the annual meeting of the American Academy of Allergy, Asthma and Immunology.

Likewise, those patients with Medicaid insurance and recent respiratory-related medical visits were more than twice as likely to have uncontrolled asthma, with adjusted odds ratios (OR) of 2.44 and 2.37, respectively. Dr. Stanford is the director of U.S. Health Outcomes at GlaxoSmithKline.

The study included 1,902 adult patients from primary care practices around the country. Before seeing their physicians, participants completed a brief, self-administered questionnaire that included questions about asthma control, patient demographics, individual health behaviors, patient medical history, asthma exacerbation history for the last year, and reason for seeing their primary care physician.

A total of 50% of participants had mild asthma, 44% had moderate asthma, and 6% had severe asthma.

In all, more than half of the patients (57%) had uncontrolled asthma. Overall, 40% of patients were seeing their primary care physicians for respiratory-related visits.

Asthma exacerbation in the last year, use of medications for nasal allergies, and exposure to secondhand smoke were dropped from the final model, while sex, age, and race were added to the model.

Other factors associated with increased likelihood of having poorly controlled asthma included the presence of gastroesophageal reflux disease/acid reflux/chronic heartburn (OR 1.44), current smoker status (OR 1.83), and body mass index greater than 30 kg/m^2 (OR 1.54). ■

ICU Patients in Danger of Injected Drug Errors

BY MICHELE G. SULLIVAN
Elsevier Global Medical News

One-third of patients hospitalized in intensive care units experienced at least one parenteral medication error during a single 24-hour period, with some suffering permanent injury and even death as a result of the mistakes, a prospective study has shown.

The medication errors were associated with increasing complexity of illness, demands on nursing care, and increasing numbers of injected drugs, Dr. Andreas Valentin and his colleagues reported in BMJ (2009 [doi:10.1136/bmj.b814]).

The data, based on a self-report questionnaire, give only a glimpse into what might be an even greater problem, wrote Dr. Valentin, director of the intensive care unit at the Medical University of Vienna. "Considering that this number ... might underestimate the frequency and consequences of errors, these results might be of even greater clinical significance," Dr. Valentin and his colleagues wrote. "Our study shows that the administration of parenteral medication is a weak point in patient safety in intensive care."

The study included 1,328 patients in 113 intensive care units in 27 countries, including 2 in the United States. During the 24-hour study period, staffs were asked to fill out a single questionnaire at the bedside of each patient. The survey asked if, and at what time, any parenteral medication error had occurred.

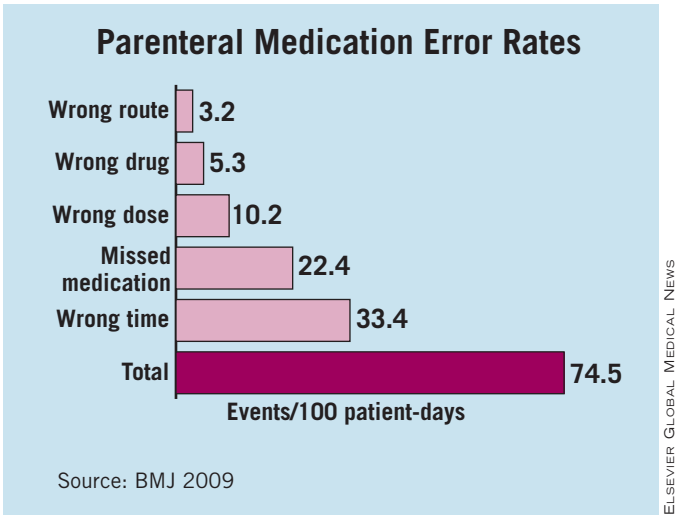
The patients' median age was 62 years. The median Sepsis-Related Organ Failure Assessment (SOFA) score was 5, indicating dysfunction in one organ system. Nursing manpower was estimated as well. The median score was 27, indicating that a given patient would consume 59% of the workload that one unit nurse could perform in 24 hours.

Among the 1,328 patients, 861 medications errors affecting 441 patients were reported; 250 patients experienced one error and 191 experienced more than one. That translated to a rate of 74.5 errors per 100 patient-days. Of the 113 units in the study, only 21 (19%) reported no medication errors.

The most frequent errors were medications given at the wrong time (386), followed by missed medications (259), wrong dose (118), wrong drug (61), or wrong route of administration (37). Most of the mistakes occurred during routine care (69%); only 4% occurred during emergencies and 3% during an urgent crisis with another patient in the unit. Staffs reported that workload and stress contributed to 32% of errors.

The errors resulted in no change in status for 71% of the patients involved. However, seven patients were permanently harmed, and five patients died as a result of mistakes.

A multivariate analysis showed that every instance of organ failure increased the risk of medication error by 19%; for each additional patient on a nurse's roster, the risk increased by 30%.



One of the most significant factors was administering a medication that had been prepared by a pharmacist, which nearly tripled the risk of a medication error (odds ratio 2.6). "In contrast," the authors wrote, "the risks for such an event were lower when nurses labeled syringes that they themselves had prepared. This can be seen as an example of reducing complexity and avoiding gaps in information and communication in the process of care by preparing medication at the place where it is needed."

Factors that significantly decreased the risk of errors were the presence of an existing critical incident reporting system (31% decrease), and routine medication checks at shift change (32% decrease).

A few easily implemented changes could help reduce the number of errors, the authors suggested. ICUs should have a critical incident reporting system and routine checks of perfusors and infusion pumps at every shift change. In addition, "Unit administrators should be aware that an increasing number of beds and an increasing ratio of patients to nurses are risk factors for occurrence," the researchers noted. ■

Central Line–Associated MRSA Decreasing in ICUs

BY MARY ANN MOON
Elsevier Global Medical News

The incidence of methicillin-resistant *Staphylococcus aureus* bloodstream infections related to the placement of central lines has declined in recent years in all major types of adult ICUs and has remained stable in non–neonatal pediatric ICUs, according to a recent report.

These findings suggest that prevention efforts are succeeding for this subgroup of MRSA patients, said Dr. Deron C. Burton and associates at the Centers for Disease Control and Prevention.

To characterize trends in MRSA incidence, the researchers assessed surveillance data reported to the CDC by 1,684 ICUs in 43 states during 1997-2007. In all, 33,587 central line–associated bloodstream infections were reported, of which 2,498 (7%) were MRSA.

The incidence of central line–associated bloodstream MRSA infections rose in 1997-2001, but declined through 2007, resulting in an estimated decline of approximately 50% over the entire study period, the investigators said (JAMA 2009;301:727-36).

The incidence declined in recent years in all six major subtypes of adult ICUs: surgical; medical; combined medical-surgical without a major teaching affiliation; combined medical-surgical with a major teaching affiliation; cardiothoracic; and coronary units. For non–neonatal pediatric ICUs, the incidence of central line–associated bloodstream MRSA infections remained stable from 1997 through 2007.

In an editorial, Dr. Michael William Climo of the Veterans Affairs Medical Center, Richmond, Va., said that the decline in this specific subset of MRSA infections occurred against the backdrop of an increase in overall MRSA infections.

It is likely that this reduction was related to a range of interventions that have been implemented during the last decade, including better hand hygiene practices, adoption of standardized line insertion and care practices, proper barrier precautions, improved catheter technology, and shorter periods of indwelling catheter use in patients, Dr. Climo said (JAMA 2009;301:772-3).

The report offers "encouraging news," commented Kathy Warye, CEO of the Association for Professionals in Infection Control and Epidemiology.

The findings show that health care–associated infections "can be prevented in a very vulnerable group of patients when institutions consistently implement evidence-based prevention strategies," Ms. Warye said in a statement. Noting that 67% of MRSA cases occur outside the ICU, she urged health care leaders to "turn their attention to the ... floors where people are being treated for general medical conditions like diabetes, pulmonary and cardiac problems." ■

CHEST One of '100 Most Influential Journals'

CHEST, the official peer-reviewed publication of the American College of Chest Physicians (ACCP), has recently been selected as one of the "100 most influential journals in the world in medicine and biology" by the Special Libraries Association (SLA), an international organization with more than 11,000 members.

"Being selected as one of the 100 most influential journals is a great honor. It's a celebration and a validation of the past 75 years of trying to publish the best and most relevant topics in clinical chest medicine," said *CHEST* Editor in Chief Dr. Richard S. Irwin, FCCP. "Because *CHEST* was selected by individuals familiar with medical journals and their use-fulness to readers in libraries and institutions, we can surmise that *CHEST* is deserving of this honor because it is relevant, respected, and useful to its audience."

In celebration of its centennial, the SLA had 686 members of its Biomedical and Life Sciences Division (DBIO) identify the 100 most influential journals in medicine and biology over the last 100 years, an exclusive list known as the DBIO 100. The SLA evaluated up to 34 journals in each of three categories: clinical medicine and allied health sciences; molecular and cellular biology; and natural history. *CHEST* was not only considered to be among the DBIO 100 but also among the 33-34 most influential journals in clinical medicine and allied health sciences. *CHEST* also was the only respiratory or respiratory-related journal chosen in this elite group, beating the second-place respiratory journal by three times the number of votes, and stands among other revered journals, such as *Cell*, *Circulation*, *JAMA*, *Nature*, *New England Journal of Medicine*, *Science*, and *The Lancet*.

"Sharing this honor with some of the world's top medical journals is very humbling and energizing at the same time and provides us with a great sense of pride," said Dr. Irwin. "It is also a validation of our strategy to provide our readers what they need. We hope this is a harbinger of even greater things to come."

Published since 1935, *CHEST* is known for providing cutting-edge, and often provocative, clinical research in the areas of pulmonary, critical care, thoracic surgery, cardiorespiratory interactions and, more recently, sleep medicine. This dedication to providing readers with the most current knowledge in chest medicine has kept journal content fresh and exciting and leaves readers anticipating their next issues.

"The DBIO Top 100 designation reinforces our commitment to publishing a highly respected and relevant peer-reviewed medical journal that gets to the heart— and lungs— of ACCP's vision of being the leading resource for the improvement of cardiopulmonary health and critical care worldwide," said *CHEST* Executive Editor Stephen J. Welch. "Because the journal is arguably the most visible and tangible product of the ACCP, this award enhances the reputation of the ACCP and should be a great source of pride for ACCP members."

In the last decade alone, *CHEST* has added several new features to keep up with reader demand and to adapt to changing technology. In 2007, *CHEST* launched its extensive archiving system, where subscribers can research *CHEST* articles as far back as 1935 free. And, just this year, *CHEST* launched its Interactive Physiology Grand Rounds, enabling readers to manipulate specialized medical procedures animated on screen through the online version of the journal.

"As we know from ACCP's March 2009 Continuing Medical Education Guideline, straight didactic formats are not the most effective ways to provide education that will change behavior and improve outcomes," said Mr. Welch. "We must continue to innovate the way we convey information via technology so that our readers and users are getting a more multifaceted, multimedia learning experience."

As the ACCP approaches its 75th anniversary celebration at CHEST 2009, in San Diego, Oct 31 to Nov 4, the ACCP and the journal have embarked on an initiative to commemorate 75 years of exceptional medical research published in the journal.

Guest editors Dr. Loren J. Harris, FCCP, and Dr. Glenn Tillotson, FCCP, will identify the top 75 articles from the past 75 years of *CHEST*. These landmark articles—in the areas of tuberculosis, lung cancer, sepsis, thoracic and cardiac surgery, critical care, sleep apnea, and more—will be featured in a special 75th anniversary monograph to be released at CHEST 2009.

"For 75 years, *CHEST* has embodied the unique quality of combining a focused clinical orientation with a multidisciplinary coverage of topics. It truly reflects the ACCP's mission of improving patient care through education," said *CHEST* Publisher Alvin Lever, MA, FCCP(Hon). "The combination of expert commentaries, high-quality clinical research, reviews of current topics, and case-based educational sections has developed over the years and been tweaked by each editor. And we're not done yet."

The SLA is a nonprofit global organization for innovative information professionals and their strategic partners. SLA serves more than 11,000 corporate, academic, government, and other information specialists in 75 countries.

To learn more about the SLA or the award, please visit http://units.sla.org/division/dbio/publications/resources/dbio100.html. ■

This Month in *CHEST*: Editor's Picks

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

▶ **Predictors of Habitual Snoring and Obstructive Sleep Apnea Risk in Patients With Asthma.** *By Dr. M. Teodorescu, FCCP, et al.*

▶ **Oropharyngeal Cleansing With 0.2% Chlorhexidine for Prevention of Nosocomial Pneumonia in Critically Ill Patients: An Open-Label Randomized Trial With 0.01% Potassium Permanganate as Control.** *By Dr. T. S. Panchabhai, et al.*

▶ **Antibiotic Prescribing and Outcomes of Lower Respiratory Tract Infection in UK Primary Care.** *By Dr. C. C. Winchester, et al.*

TRANSPARENCY IN HEALTHCARE

▶ **Reducing Iatrogenic Risk in Thoracentesis: Establishing Best Practice via Experiential Training in a Zero-Risk Environment.** *By Dr. D. R. Duncan, et al.*

RECENT ADVANCES IN CHEST MEDICINE

▶ **Thrombolytic Therapy for Acute Pulmonary Embolism: A Critical Appraisal.** *By Dr. J. L. Todd, and Dr. V. F. Tapson, FCCP*

www.chestjournal.org

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

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)]*.

Dr. Bird Receives the Presidential Citizens Medal

Dr. Forrest Bird, the inventor of the first modern respirator, can now add the honor of receiving the Presidential Citizens Medal to his many accomplishments. In December 2008, President George W. Bush awarded Dr. Bird with the Presidential Citizens Medal—one of the highest honors the President can confer upon a civilian, second only to the Presidential Medal of Freedom. This honor was established in 1969 to recognize US citizens who have performed exemplary deeds of service.

The ACCP and CHEST Foundation congratulate Dr. Bird on receiving this high honor and are grateful to Dr. Bird for allowing The Foundation to be included among those that have recognized him for his exceptional career in the field of respiratory medicine. At CHEST 2008 in Philadelphia, Pennsylvania, The CHEST Foundation recognized Dr. Bird, who is a physician, pilot, and inventor of the Bird Mark 7, one of the first modern respirators. The Foundation also established the Forrest M. Bird, MD, PhD, ScD Endowment in Mechanical Ventilation to honor him and his life-saving contributions to advance mechanical ventilation. At the Making a Difference Awards Dinner, Dr. Bird's family, friends, and colleagues paid tribute to him for his outstanding career as an inventor and his numerous achievements in the area of respiratory medicine.

If you wish to donate to the Forrest M. Bird, MD, PhD, ScD Endowment in Mechanical Ventilation, please contact Teri Ruiz at truiz@chestnet.org, or visit www.chestfoundation.org, select the Make A Donation icon, and click the Donations link under Forrest M. Bird MD, PhD, ScD Endowment in Mechanical Ventilation.

THE CHEST FOUNDATION℠

Making a Difference Awards Dinner

Save the Date—The CHEST Foundation's 11th Annual Making a Difference Awards Dinner will take place on Saturday, October 31, 2009, 7:00 PM – 10:30 PM, at the Manchester Grand Hyatt, San Diego, California.

This year's event will feature a celebration of the 75th anniversary of the ACCP—75 years of inspiration for its members and their patients. In addition, the Alvin Lever, MA, FCCP(Hon), and Norine Lever, PhD Honorary Endowment will be announced, and The Foundation will also recognize ACCP members' pro bono service by conferring the D. Robert McCaffree, MD, Master FCCP Humanitarian Awards to those members with winning humanitarian service projects from around the world.

Registration will begin July 1, 2009, at www.chestfoundation.org. Price per ticket is $150. Please contact Teri Ruiz at truiz@chestnet.org.

ACCP Leaders Take the Challenge

The CHEST Foundation is working to increase participation from leadership by engaging them with fundraising on The Foundation's behalf. This year, The CHEST Foundation's Development Committee has established two separate challenges—the ACCP Governors' Challenge and the ACCP NetWorks' Steering Committee Challenge. The ultimate goal of these two challenges is to increase awareness of The Foundation's four areas of focus: tobacco prevention, humanitarian service, clinical research, and critical care/end-of-life care.

Although these challenges were announced this spring, the donor gift tracking for both challenges will be retro-active to July 1, 2008, and will run through September 30, 2009. These challenges will work in the following way:

- Governors in the United States and Canada who accept the challenge will help fund raise by contacting members from their states and provinces who have not yet donated in the current fiscal year.
- NetWork Chairs who accept the challenge will help fund raise by contacting their NetWork's Steering Committee members who have not yet donated in the current fiscal year.
- Participating Governors and NetWork Chairs will be asked to fund raise by letter, e-mail, and phone. The minimum request will be for a $100 annual gift. Contact information, solicitor scripts, and fact sheets about The CHEST Foundation will be provided. All Governors and NetWork Chairs are encouraged to engage other members to help them in this effort.
- Donor recognition will be immediate, with Governors and NetWork Chairs sending either personalized notes to their contacts who have donated, or they can choose to be a cosigner of The Foundation's tax-deduction thank you letter.
- Monthly summary data will be provided by The CHEST Foundation for the Council of Governors and Council of NetWorks to review. In addition, each participating Governor and NetWork Chair will be provided with month-end status reports.
- Winners of both challenges will be determined based upon a ratio of the number of possible donors vs actual number donating.
- The winning fund raisers for the Governors' Challenge and the NetWorks' Steering Committee Challenge will each be provided with four free tickets to the 11th Annual Making a Difference Awards Dinner and will be featured in articles in The CHEST Foundation's newsletter, *Extraordinair,* and in the ACCP's *CHEST Physician*. ■

CHEST 2009 in San Diego: Nice Weather We're Having

The US Weather Bureau describes San Diego's climate as the most nearly perfect in America. It can be characterized as Mediterranean-like, with warm winters and cool summers. The typical San Diego weather forecast of "sunny and mild" is one reason why so many people love to visit and another why you'll want to attend CHEST 2009.

What makes the San Diego climate so perfect? The prevailing breezes from the Pacific Ocean temper the weather in San Diego and protect it from extreme weather conditions. It is uniquely located to avoid the summer monsoons that blow south across Mexico and Arizona. Since the jet stream usually tracks north of San Diego, it rarely experiences heavy rainfall or violent winter storms.

The potential for a favorable forecast is a plus when deciding "weather" to attend CHEST 2009. If you're coming from an area with less favorable weather conditions, you can expect milder, more pleasant conditions as you take advantage of the year's best learning opportunity in clinical chest medicine.

CHEST 2009
October 31 - November 5
San Diego, California

CHEST 2009 takes place in San Diego, California, 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.

CHEST 2009 also marks the start of a year-long celebration of the ACCP's 75th anniversary—75 years of inspiring leadership, education, clinical practice, and communication. Watch for special celebrations and events. Early registration fees for CHEST 2009 are in effect now, and ACCP members can save up to $155. Register at www.chestnet.org. ■

CHEST Challenge: There's Still Time!

Win paid registration, travel, and hotel for CHEST 2009 by participating in CHEST Challenge. Game ends May 31.

Visit www.CHESTChallenge.org.

Pulmonary Perspectives

Alpha$_1$-Antitrypsin Deficiency

Alpha$_1$-antitrypsin deficiency (AATD) is the most well characterized genetic risk factor for COPD. However, this is a rare disease with the frequency of the PiZZ or PiSZ severe deficiency state present in 0.5 to 3% of patients with COPD.

Guidelines by the ATS/ERS/ACCP suggest testing for all patients with COPD and for patients with asthma who fail to completely respond with normal spirometry values while receiving optimal therapy.

Although I personally follow the recommendations to test these populations as a routine part of my practice, I must admit that I get frustrated at times. National averages would suggest that I must test 100 patients with COPD to find one AATD-affected individual. I understand the heterogenous response to testing from the pulmonary community.

One response has been to test only those individuals with early-onset COPD or with a basilar-predominant emphysema. We now know that this selection bias will miss more than 50% of patients with AATD. Campos and colleagues[1] recently showed that 30% of individuals with AATD were age >60. These patients had typically smoked less than younger AATD patients. Parr et al,[2] in a study of CT patterns in AATD, showed that while basilar predominant emphysema is the most common CT presentation in AATD, clinically significant bronchiectasis was demonstrable in 27%. The NHLBI registry study showed a frequency of cough and sputum production consistent with chronic bronchitis in 50% of individuals.[3] Clearly, these data show that attempts to clinically phenotype patients with COPD as having or not having AATD have no evidence-based data that support the practice.

One alternative to physician testing is birth testing for this genetic disease. Birth testing will require pilot trials to define the costs and benefits of this practice. The most clearly defined benefit in studies to date performed in Sweden from 1972 to 1974 was the impact on teenage smoking rates that has allowed these individuals to maintain normal lung function to age 30.[4] Until birth testing has been shown to improve medical outcomes, testing remains in the physician's domain.

The costs of testing are not small when applied to the estimated 24 million individuals with COPD in the United States. The most cost effective population screening test is an alpha-1 antitrypsin level. This test is done at hundreds of hospitals and laboratories across the United States and, generally, can be performed for less than US $20. An alpha$_1$ level < 58 mg/dL (the equivalent level of 11 micromolar since the AAT protein is a 52 kD protein) would then require further testing to define the genotype. Genotyping should be required in COPD screening in < 3% of cases. Genotyping is a more costly test (greater than US $100) in which polymerase chain reaction technology is used to determine the number of copies of at risk S or Z alleles at the protease inhibitor (Pi) locus. This test is available from some pharmaceutical companies that cover the cost of testing. Genotype testing is also required to accurately inform family members of their genetic risks.

TESTING MAKES A DIFFERENCE IN THE LIVES OF THE AFFECTED PATIENTS AND SHOULD BE DONE MORE COMPREHENSIVELY.

Since AATD is a genetic disease and genes don't change, it is obvious that testing need be performed only once in a lifetime. The current push to develop communication tools to inform physicians when testing has been previously performed should benefit the estimated 5,000 genetic diseases like AATD that should not require repeated testing. Therefore, some COPD clinics use chart markers or other strategies to determine which patients with COPD have been previously tested for AATD.

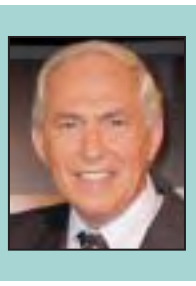
It is my opinion that comprehensive targeted testing for AATD should be performed in the United States. The benefits of testing include more than a discussion of the utility of IV augmentation therapy. Those of us with an active AATD clinic population recognize this community as an empowered group of individuals. Current data suggest that this genetic diagnosis enhances smoking cessation.[5] Individuals with AATD may choose to join disease management groups that have been shown to improve COPD outcomes, reduce ED visits, and improve SF-36 quality of life scores.[6] Importantly, these benefits come, in part, from the community of patients with AATD. This requires that your patients reach out to join the communities available to them that are sponsored by three not-for-profit organizations in the United States: The Alpha-1 Association, Alpha-1 Foundation, and AlphaNet.

Individuals with severe AATD or the PiMZ carrier state are invited to join the Alpha-1 Foundation Research Registry that is housed at the Medical University of South Carolina since 2000. The registry has grown steadily throughout the years and now enrolls more than 3,300 individuals who are willing to consider possible research studies. Future research is accelerating toward proving the safety and efficacy of inhaled alpha$_1$-antitrypsin (AAT) products. These studies will strive to prevent COPD progression, and, therefore, will require multiple years of study with large patient numbers. This challenge is problematic in rare diseases like AATD without the infrastructure that a registry provides. Registry participants are also available for recruitment to more general COPD studies. The Web site at www.alphaoneregistry.org provides further details with instructions for patients or researchers to utilize this important resource.

If the test for AATD was difficult to perform, had a high rate of false-positive results, or did not have guidelines to support use, then many of us in the pulmonary community would understand why the disease is underdiagnosed. However, the delay in diagnosis still remains too long for too many patients for most pulmonary diseases.

Therefore, other strategies are being explored to remove the human element from the decision to test for AATD. Current studies empowering the pulmonary function laboratory staff to test patients with obstruction for AATD are ongoing. The study of whether computer reminders help improve testing is ongoing at many hospitals.

Testing makes a difference in the lives of the affected patients and should be done more comprehensively. Please invite your patients with AATD to take advantage of the resources available to them to improve their COPD management. ■



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

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Dr. Charlie Strange, FCCP
Professor of Pulmonary and Critical Care Medicine
Medical University of South Carolina
Charleston, SC

Editor's Insight

I have a confession to make. I have never identified a patient with alpha$_1$-antitrypsin deficiency. The cynic would respond by saying that is because the disease is so unusual. It is an unusual disease, possibly occurring in 1 of every 100 to 200 patients with COPD.

However, I know that the real answer is that I have not screened patients as often as I should. Professor Strange makes a very important point when he emphasizes that we cannot identify these patients by a certain clinical phenotype. He also refers to the recent article by Campos and colleagues who reviewed clinical characteristics of 922 patients receiving augmentation therapy.

The average age at diagnosis of these 922 patients was 45.5 years, and many older patients had markedly prolonged delays (years and decades) before the diagnosis was established.

For any practicing pulmonologist, Professor Strange's recommendation to screen often should be heeded. The screening approach is well standardized, simple, relatively inexpensive, and accurate. The implications for the patient and family members of establishing this diagnosis are important.

Also to be emphasized is Dr. Strange's reference to the Alpha-1 Foundation Research Registry. Encouraging patient participation in this registry may be an important way forward in designing future research projects for this disease.

SLEEP STRATEGIES

Pregnancy and Sleep Disorders: We Have Much To Learn

Snoring and sleep apnea are relatively uncommon in premenopausal women. However, the incidence of sleep apnea and other disturbances markedly increases during pregnancy.

We think of pregnancy as a normal physiologic, low risk time. However, preeclampsia (PIH) occurs in 6% or more primipara women. There is mounting evidence that obstructive sleep apnea (OSA) may play a very important role in the pathogenesis of PIH. Since continuous positive airway pressure (CPAP) is a highly effective therapy for OSA, a real opportunity to improve the dire consequences of PIH exists.

Estrogen increases rapid eye movement (REM) sleep, decreases sleep latency, and decreases wakefulness after sleep onset. It also increases total sleep time. Progesterone has its effects primarily on non-REM sleep. A sedating effect, similar to that experienced with benzodiazepines, is attributed to progesterone. Sleep latency and wakefulness after sleep onset are decreased by the progesterone effect.

Changes in sleep cycle (*eg*, worse sleep, lower efficiency as a response to the hormonal changes) are worsened in 15% of women in relation to the menstrual cycle. A menstrual period hypersomnia has been described, as well. It begins soon after menarche and then recurs in 6- to 10-day episodes.

Poor sleep becomes the rule rather than the exception for many pregnant women. In one study, 68% of women reported a change in sleep pattern—especially in the third trimester (Schweiger. *Am J Obstet Gynecol* 1972; 114:879). Etiologic factors include a rise in progesterone and consequent fatigue, body temperature rise, respiratory rate rise, and frequent need to urinate.

There are important physiologic changes due to elevation of the diaphragm from abdominal mass effect and due to the increased vascular load from a one-third increase in blood volume. Sleep architecture worsens during pregnancy, with effects beginning at 12 weeks and extending into early postpartum. REM decreases, increased awakenings occur, and sleep efficiency drops.

Mindell and Jacobson (*J Obstet Gynecol Neonatal Nurs* 2000; 29:590) surveyed 127 consecutive pregnant patients and found a large percentage experienced sleep disturbance. Onset of snoring was up to 31% by the third trimester. Restless sleep and awakenings were very common. In addition, symptoms of periodic limb movement disorder were reported in 26.5%. This is likely due to pregnancy-related iron deficiency.

There is a possible association of sleep deprivation and premature labor. In addition, new-onset snoring is associated with fetal growth retardation, decreased APGAR scores, and increased fetal complications.

Snoring is more common in men than in women. Even among habitually snoring women, apnea-hypopnea index (AHI) values are much lower than in men. OSA is present in 2 to 8% of all women and slightly lower values are found in women of childbearing age. Snoring occurs in 4% of women prior to pregnancy, but its incidence increases to 25% in pregnant women.

Changes in pregnancy that influence the development of OSA include gestational weight gain, nasopharyngeal and upper airway edema, and drop in functional residual capacity due to diaphragm compromise and mass effect and increased arousals. There are mitigating pregnancy changes that decrease OSA risk. However, the balance

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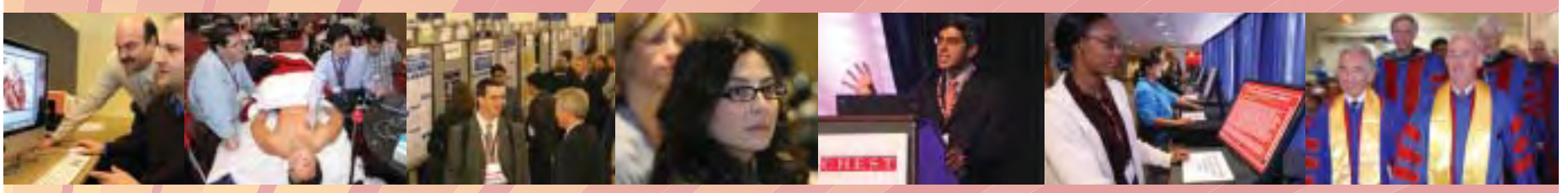
Dr. James Parish, FCCP
Section Editor,
Sleep Strategies

Sleep Institute
American College of Chest Physicians



EDUCATION INSIGHTS

Effectiveness of CME: An Evidence-Based Approach

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

What value do physicians currently place on continuing medical education once they have advanced into their career path? Is CME effective today and does physician lifelong learning really affect patient care by improving clinical knowledge, performance, and patient outcomes? Is CME simply a system to help physicians fulfill a requirement, or does it effectively improve physician practice leading to better health care? These are not new questions, but, over the years, there have been some interesting developments.

This has led to a March 2009 ACCP publication of an evidence-based guideline (*Chest* 2009; 135:1S-75S) that makes recommendations on the effectiveness of CME. This initiative began in 2005, when the ACCP proposed and obtained acceptance from the Agency for Healthcare Research and Quality to identify and synthesize the evidence for the effectiveness of CME. The results primarily focus on physician learners who have completed training, and upon whether CME is still effective for these learners. The guideline represents an important first step in critically analyzing the CME efficacy and delivery.

These areas represent important issues for the growing global emphasis on CME as a key factor driving maintenance of certification, maintenance of licensure, and quality improvement. Two of the most important findings were the identification of differences in terminology used in CME activities and in conducting CME research. Examples of terminology variation include the terms used to define a number of areas throughout the educational teaching methodologic process.

ACCP's guideline also focused upon formative assessment, as opposed to summative education and evaluation. Summative assessments review performance at some point in time but are not designed to help the physician learner during the educational process. Formative assessment, however, occurs when the physician learner is given feedback in a way that enables improved learning or performance. Formative assessment can significantly affect physician learning by affording the opportunity to evaluate and self-assess knowledge, skills, judgment, and professional values, helping to identify gaps in knowledge or skills and to encourage lifelong learning. This process allows feedback to physician learners that they are providing standards of care for their patients and advances positive changes in standards of care.

By contrast, the use of traditional lecture-based education as the only means of instruction does not provide a formative process to bring change to physician knowledge, behavior, or clinical care; lecture-based instruction alone has proved the least effective way to learn. Evidence review has shown that incorporating formative assessment into CME activities, using diversified teaching modalities, is the most effective method. Which teaching combination and how much intensity are yet to be determined.

The field of CME is changing rapidly, for both the physician educator and learner. The ACCP evidence-based guideline on effectiveness of CME provides an extensive review, recommendations, and a foundation for what the immediate future will look like. For more information on this guideline, go to www.chestjournal.org. ■

Continued from previous page

is definitely tilted to an increase in snoring and OSA in pregnant women.

Franklin et al (*Chest* 2000; 117:137) found that prior habitual snorers had an increased incidence of hypertension and/or PIH during pregnancy than did case-matched nonsnoring control subjects. Fetal size for gestational age and APGAR scores were less than those for control subjects.

PIH occurs in 6 to 8% of all pregnancies. Perinatal mortality increases fivefold in patients with PIH (Dekker. *Clin Obstet Gynecol* 1999; 42:422). OSA in pregnancy is thought to be important in the pathogenesis of PIH. It is hypothesized that placental development (and perhaps underperfusion) is a critical factor in the pathogenesis of PIH. Oxidative stress may lead to release of various factors that may then lead to endothelial dysfunction. The coagulation system is activated; microvascular angiopathy develops, as well as vasoconstriction, resulting in onset of edema, hypertension, or worse.

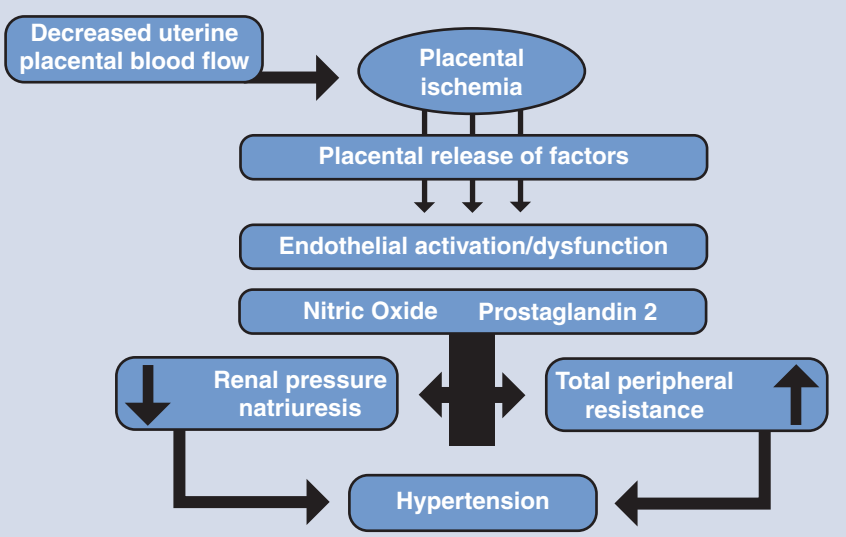
So a putative mechanism could be viewed as outlined in the figure below.

Yinon and colleagues (*Eur Respir J* 2006; 27:328) demonstrated that the AHI is abnormal in patients with PIH as compared with matched control subjects. There are early reports of the efficacy of CPAP therapy in pregnant patients with OSA and, perhaps, in modulating PIH (Edwards et al. *Am J Respir Crit Care Med* 2000; 162:252). A small study by Guilleminault and colleagues (*Sleep Med* 2007; 9:9), in which early CPAP was used in first trimester women with PIH risk factors, showed a reduction in maternal AHI but no change in maternal fetal outcomes. A second study by the same group (*Poyares et al. Sleep Med* 2007; 9:15) did show improved blood pressure control, as well as improved fetal outcomes in a group of high risk patients treated with nasal CPAP.

Women have a higher incidence of sleep disorders than is currently recognized in clinical practice. There are many reasons for worsened sleep during pregnancy. Awakenings are common, as is the occurrence of periodic limb movement disorder. The incidence of snoring and obstructive sleep apnea increases significantly in pregnancy. OSA in pregnancy has significant consequences and may be an important component in the pathogenesis of PIH. This is a fertile area for future research. ■

Dr. Antoinette Williams
Assistant Professor, and
Dr. James A Barker, FCCP,
Professor and Chief
Division of Pulmonary/Critical Care/Sleep Disorders
University of South Carolina School of Medicine at Palmetto Richland Hospital
Columbia, SC

Pathogenesis of preeclampsia



ACCP Members Visit Capitol Hill for Annual Caucus

On March 9-10, 2009, more than 60 ACCP members descended on Washington, DC, for the 16th Annual ACCP Capitol Hill Caucus. Attendees met with 185 Senate and Representative offices to urge legislators to address the critical care workforce shortage and highlight the importance of the US Food and Drug Administration (FDA) having meaningful authority to regulate tobacco products.

On day 1, participants gathered at the Fairfax at Embassy Row to receive background information regarding the priority legislative issues for chest medicine and organized medicine generally. Guest speakers included Meg Riordan, Campaign for Tobacco-Free Kids; Todd Askew, American Medical Association; Phil Porte, NAMDRC; and ACCP's legislative counsel, Michael Gaba, Esq, Holland & Knight.

Attendees also received insider tips and techniques to help influence elected officials from "Advocacy Guru," Stephanie Vance. The dinner speaker featured Kathie Kendrick, MSCS, BSN, Deputy Director of the Agency for Health Research and Quality (AHRQ), who discussed current AHRQ priorities, including a new emphasis on comparative effectiveness research.

The following morning participants reconvened on Capitol Hill to gain insights into the inner workings of congressional offices from Erika Orloff, Senior Legislative Assistant for Health Care for Representative Bart Stupak (D-MI-1), and Cheryl Jaeger, Senior Policy Advisor to House Republican Whip Eric Canter (R-VA-7).

Jeffrey Teitz, Chief Counsel for Policy to Senator Edward Kennedy (D-MA), also spoke to attendees regarding the *Family Smoking Prevention and Tobacco Control Act*, which, if enacted, would, for the first time, grant authority to the FDA to regulate tobacco.

Dr. Maria Jison, FCCP, Mid-Atlantic Pulmonary Clinic, Kensington, Maryland, commented that "the Caucus continues to be a great experience. Each year I go, I learn more and want to be even more involved. This year, the third for me, I learned even more the importance and effectiveness of having an ongoing relationship with the legislative office."

Dr. Dennis Moritz, FCCP, ACCP Governor for West Virginia, described the Caucus as "one of the best learning experiences that I ever had - I cannot wait to get home to share all my new knowledge of these topics with my associates - and not just ACCP members, but all folks involved in medicine."

Coinciding with the Caucus was a new ACCP eAdvocacy campaign, in which ACCP members who were not able to attend the Caucus were asked to amplify our message on the Hill by e-mailing messages to their own Representatives and Senators regarding the legislative priorities discussed at the Caucus. We had an enthusiastic response from members to support our message

Also new this year was the development of three advocacy podcasts that discuss the critical care workforce shortage, FDA regulation of tobacco, and the Obama health-care plan. The podcasts are available on the ACCP Grassroots Advocacy Web site at www.chestnet.org/advocacy. Also, visit this site soon for information on the 17th Annual ACCP Capitol Hill Caucus in spring 2010. ■

ACCP WORLDWIDE

1st International ACCP Pulmonary Board Preparation and Review

June 24-28, 2009
Athens, Greece

This intensive education program, organized by the Hellenic Thoracic Society in collaboration with the ACCP, is developed from the successful ACCP pulmonary board review course. With more than 30 years' experience delivering board review curriculum, the ACCP is recognized as a proven leader in the field.

Developed by world-renowned clinicians, the course will feature 32 state-of-the-art lectures on the major topics in pulmonary medicine presented by distinguished professors from the United States and Greece. This is an excellent review opportunity for young health-care professionals, as well as established practitioners who want to update their clinical knowledge.

The organizing committee is headed by Dr. Panagiotis K. Behrakis, FCCP, and Dr. Mark J. Rosen, FCCP, and the faculty chairs are Dr. Stephanie M. Levine, FCCP, and Dr. Konstantinos L. Gourgoulianis.

For updated information, go to www.chestnet.org/education/courses/endorsed/june/index.php.

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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.

Rx only

Rev. May 2008

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*.

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Please see brief summary of prescribing information on adjacent page.