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CHEST Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

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The results show that PET/CT can replace conventional staging in early-stage non–small cell lung cancer, said Dr. Donna E. Maziak.

PET/CT Accurate When Staging Early NSCLC

BY FRAN LOWRY
Elsevier Global Medical News

CHICAGO — In patients with early-stage, biopsy-proven non–small cell lung cancer, the combination of ^{18}fluorodeoxyglucose (FDG)–PET/CT and cranial imaging can reduce stage-inappropriate surgeries by providing more accurate staging than conventional imaging, a randomized trial suggests.

Investigators randomized 163 patients with biopsy-proven non–small cell lung cancer who were felt to have resectable disease (on the basis of physical examination, computed tomography of the chest, or a chest x-ray) to conventional staging (CT scan of the abdomen, bone scan, and brain imaging by CT or MRI), or to positron emission tomography staging (whole-body PET/CT scan and cranial imaging by CT or MRI), Dr. Donna E. Maziak, FCCP, reported at the annual meeting of the American Society of Clinical Oncology.

Of the patients who were randomized to whole-body PET/CT, 23 (14%) were correctly upstaged, which prevented stage-inappropriate surgery, compared with 11 (7%) of 157 patients randomized to conventional imaging (P = .046). The eight-center trial also found that conventional imaging erroneously understaged 47 (30%) patients, whereas whole-body PET/CT erroneously understaged 18 (11%) patients (P = .00003).

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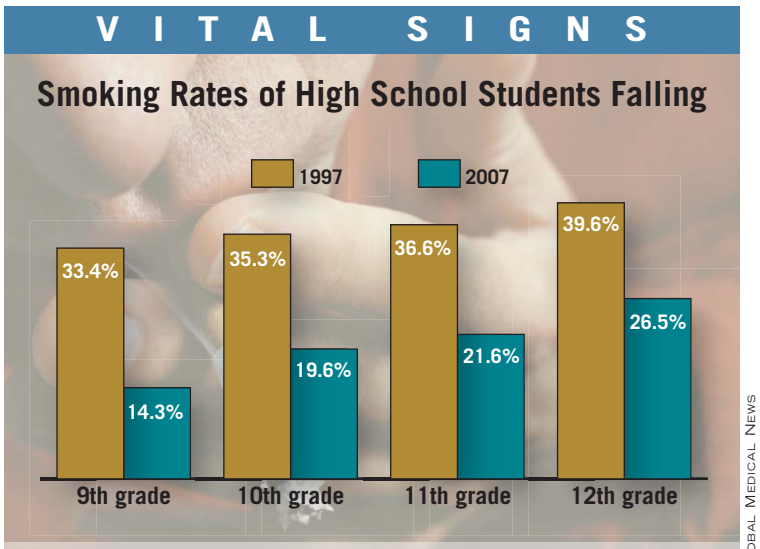
VITAL SIGNS



Note: Based on data from the Youth Risk Behavior Survey for students reporting smoking cigarettes on at least 1 day during the 30 days prior to the survey.
Source: Centers for Disease Control and Prevention

ELSEVIER GLOBAL MEDICAL NEWS

ACCP Unveils Updated Thrombosis Guidelines

First major revision since 2004.

BY BETSY BATES
Elsevier Global Medical News

Sweeping new clinical guidelines issued by the American College of Chest Physicians provide updated recommendations on how to prevent and manage thrombosis in surgical patients and special risk groups, including pregnant women, children, obese patients, and patients with prosthetic heart valves or a history of cardiovascular disease or stroke.

Separate sections address patients with inherited thrombophilias and treatment of deep vein thrombosis and pulmonary embolism.

Unveiled in the June issue of CHEST, the guidelines represent the first major revision in the recommendations since 2004. Compiled by more than 90 experts, the 700 recommendations run more than 1,000 pages, although a concise, 38-page executive summary is available (Chest 2008;133:71S-109S).

In accordance with many new clinical guidelines, grades are assigned to each recommendation or suggestion, based on the quality of the available evidence and the strength of the recommendation.

Among the most noteworthy recommendations is a renewed call for venous thromboembolism (VTE) prophylaxis of most hospitalized patients.

"For every general hospital, we recommend that a formal, active strategy that addresses the prevention of VTE be developed … in the form of a written, institution-wide thrombo-prophylaxis policy," the guidelines state.

Computer decision support systems, preprinted orders, and periodic audits and feedback mechanisms are advocated by the committee, while "passive methods" such as educational meetings and handouts are deemed inadequate as stand-alone strategies to increase adherence to thromboprophylaxis.

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Vaccinate for IPD in Adults With Asthma

BY MIRIAM E. TUCKER
Elsevier Global Medical News

ATLANTA — All adults with asthma should now receive pneumococcal immunization, the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention voted June 25 at its summer meeting.

The vote adds adults aged 18-64 years with asthma to the list of individuals considered at increased risk for invasive pneumococcal disease (IPD).

Current Advisory Committee on Immunization Practices (ACIP) recommendations call for use of the 23-valent polysaccharide pneumococcal vaccine (PPSV23) in all adults age 65 years and older and in high-risk individuals age 2-64 years. Among the latter group are those with chronic pulmonary conditions including chronic obstructive pulmonary disease (COPD) and emphysema (MMWR 1997;46[RR-8]:1-24).

Asthma was not included at the time that recommendation was made because not enough data were available about the risk of IPD among individuals with asthma, except for those with long-term use of systemic corticosteroids. Such data have since become available, and were reviewed for the committee by Dr. Pekka Nuorti of the CDC's National Center for Immunization and Respiratory Diseases.

In a nested case-control study of persons age 2-49 years enrolled in Tennessee's Medicaid program (TennCare) for at least 1 year during 1995-2002, each

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Thrombosis

Guidelines • *from page 1*

Hospitals need to have firm policies and enforce them, said Dr. Jack Hirsh, FCCP, professor emeritus of medicine at McMaster University and founding director of the Henderson Research Center, both in Hamilton, Ont.

In the new guidelines, the recommendation for VTE prophylaxis has been expanded beyond major general, gynecologic, and orthopedic surgeries to include bariatric and coronary artery bypass surgery.

No prophylaxis is recommended for low-risk patients undergoing laparoscopic surgery or knee arthroscopy, or those taking long airplane flights.

As expected, the new guidelines reaffirm the position of the American College of Chest Physicians that aspirin alone is not sufficient therapy to prevent venous thromboembolism in any patient population, because more effective alternatives are available, including heparin, low-molecular-weight heparin, and a synthetic, selective factor Xa inhibitor, fondaparinux, which was approved by the FDA in 2001.

Many of the guidelines now mentioning fondaparinux as an alternative anticoagulant rate the evidence for its use as 1A, meaning that the supportive data are strong.

The length of recommended postsurgical prophylaxis has been extended in the guidelines to 28 days (and in some surgeries, 35 days) for most general, gynecologic, and orthopedic procedures, noted Dr. Geno J. Merli, chief medical officer of Thomas Jefferson University Hospital, Philadelphia. Previously, prophylaxis was generally advised for 2 weeks following surgery.

Among the most pivotal changes in the recommendations are guidelines on patients with atrial fibrillation, management of pregnant women and children, and treatment of DVT.

▶ **Atrial fibrillation.** Antithrombotic therapy in patients with atrial fibrillation is awarded the strongest evidence grade (1A), reflecting widespread agreement of findings from randomized, controlled trials.

Target international normalized ratio ranges, drug choices, and dosages are detailed in the new guidelines in the hopes that primary care physicians will use the document to guide therapy, Dr. Hirsh said.

"There is marked underutilization of warfarin [in atrial fibrillation patients], not by cardiologists, but by family physicians. The logistics of monitoring are difficult," he said. As a result, one entire section addresses the nuts and bolts of monitoring.

▶ **Pregnant women.** Dr. Hirsh identified new guidelines for pregnancy as among "the most controversial and, I think, the most important" in the document.

Randomized trials are difficult to conduct in this population, so most of the recommendations receive a 2C grade that reflects weak evidence, noted Dr. Shannon M. Bates, who oversaw the chapter on pregnancy issues.

Nonetheless, "a great deal of work has gone into making sure that our recommendations are unbiased and clearly reflect the available data," said Dr. Bates, director of the adult hematology residency training program at McMaster University Medical Centre in Hamilton, Ont.

Key elements of the pregnancy guidelines include a recommendation against routine prophylaxis other than early mobilization in patients undergoing Cesarean section, and deletion of a previous recommendation advocating antithrombotic therapy in women with pregnancy complications and a known inherited hypercoagulable state.

▶ **Children.** Greatly expanded guidelines "pretty well cover every conceivable thrombotic issue" in neonates and children, Dr. Hirsh noted.

Stroke is 1 of the 10 leading causes of death in childhood, but it is difficult to diagnose and predict based on risk factors. Therefore, the new guidelines recommend that any child with arterial ischemic stroke receive initial antithrombotic therapy until the underlying causes are understood, followed by maintenance therapy to prevent recurrence.

Detailed sections offer guidelines on the prevention of thrombotic events in children with congenital heart disease, including sections on ventricular assist devices and prosthetic heart valves.

▶ **Treatment of DVT.** The guidelines offer two options—one monitored and one unmonitored—for subcutaneous heparin administration for acute DVT, Dr. Merli said in an interview.

The first regimen calls for an initial dose of 17,500 U or a weight-adjusted dose of about 250 U/kg every 12 hours, with the dose adjusted to achieve and maintain an activated partial thromboplastin time (aPTT) prolongation that corresponds to plasma heparin levels of 0.3-0.7 IU/mL anti-Xa activity when measured 6 hours after injection (rather than beginning therapy with the smaller initial dose).

The second option is a fixed dose, unmonitored regimen that calls for an initial dose of 333 U/kg followed by a twice-daily dose of 250 U/kg.

The guidelines also suggest for the first time the use of catheter-directed thrombolysis with thrombus fragmentation and/or aspiration in "selected patients with extensive acute proximal DVT who have a low risk of bleeding," but advocate this pharmacomechanical approach only if "appropriate expertise and resources are available." ■

NSCLC Staging

PET/CT • *from page 1*

"These results show that [whole-body PET/CT] can replace conventional staging in early-stage non–small cell lung cancer," explained Dr. Maziak of the University of Ottawa.

The study was conducted by the Ontario Clinical Oncology Group, and funded by the Ontario Ministry of Health and the Canadian Institutes of Health Research.

The patients were matched for age (mean 67 years), Eastern Cooperative Oncology Group (ECOG) performance status, and smoking status. Half of the study population was female.

Discussant Dr. Reginald F. Munden, chair of the department of radiology at the University of Alabama at Birmingham, said the conclusion that whole-body PET/CT can replace conventional staging of non–small cell lung cancer has to be qualified.

He reminded delegates that the CT being done with PET must be done at full inspiration, so that small lesions are not missed.

"The lung windows have to be done in a diagnostic mode; otherwise, you cannot replace conventional CT with a routine PET/CT," Dr. Munden cautioned.

He added that the degree to which futile surgeries can be reduced with the use of PET/CT remains debatable.

"I suspect the reduction in futile surgeries probably has as much to do with local practice as it does with the imaging itself," he said.

"As we know, some surgeons would prefer to do mediastinoscopy on everyone," Dr. Munden added.

"Most of the studies seem to suggest there is a reduction, but the question is, Is it a significant reduction or not?" he said.

Neither Dr. Maziak nor Dr. Munden disclosed any relevant conflicts of interest. ■

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CHEST PHYSICIAN

CHEST PHYSICIAN, the newspaper of the American College of Chest Physicians, provides cutting-edge reports from clinical meetings, FDA coverage, clinical trial results, expert commentary, and reporting on the business and politics of chest medicine. Each issue also provides material exclusive to the members of the American College of Chest Physicians. Content for **CHEST PHYSICIAN** is provided by International Medical News Group and Elsevier Global Medical News. Content for NEWS FROM THE COLLEGE is provided by the American College of Chest Physicians.

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Adjuvant Cisplatin Leads to Late Mortality in NSCLC

Despite improved 5-year survival, patients on the drug were more likely than controls to die during years 6-8.

BY KERRI WACHTER
Elsevier Global Medical News

CHICAGO — Following 5 years of improved survival with cisplatin-based adjuvant chemotherapy for resected non–small cell lung cancer, investigators were surprised to find more late mortality in treated patients, compared with those randomized to observation in a large phase III study.

"We observed more deaths after 5 years in the chemotherapy arm, compared with the control arm," said Dr. Thierry Le Chevalier at the annual meeting of the American Society of Clinical Oncology, where he presented long-term data from the International Adjuvant Lung Cancer Trial (IALT).

Adjuvant cisplatin-based chemotherapy produced a significant survival advantage during the first 5 years (hazard ratio of death 0.86, $P = .01$), but treated patients were more likely to die during years 6-8, compared with control patients randomized to observation (hazard ratio of death 1.45, $P = .04$).

In the chemotherapy arm, 495 deaths occurred before 5 years and 83 deaths afterward, whereas the control group had 534 deaths before 5 years and 56 afterward.

Of note, over 8 years non–lung cancer mortality was greater in the chemotherapy arm (hazard ratio of 1.34, $P = .06$). After 5 years non–lung cancer deaths became more than twice as common in the chemotherapy arm: 25 vs. 10 in the control group.

From 1995 to 2001, the IALT Collaborative Group randomized 1,867 patients with resected, pathologically documented stage I, II, or III non–small cell lung cancer (NSCLC) at 148 centers in 33 countries—932 patients to adjuvant cisplatin (Platinol)–based chemotherapy and 935 to observation alone.

Thoracic radiotherapy of 60 Gy or less was optional (predefined by N stage at each center). Median follow-up was 7.5 years with 97% of patients in follow-up.

Centers were allowed to choose cisplatin chemotherapy of 80 mg/m^2 every 3 weeks for four cycles, 100 mg/m^2 every 4 weeks for three to four cycles, or 120 mg/m^2 every 4 weeks for three cycles.

Each center also could choose one of the following drugs for combination with cisplatin: 100 mg/m^2 etoposide on days 1-3, vinorelbine (Navelbine) 30 mg/m^2 weekly, vinblastine (Velban) 4 mg/m^2 weekly, or vindesine (Eldisine) 3 mg/m^2 weekly.

The overall survival rate at 8 years was 38% (578 deaths) in the chemotherapy arm, compared with 37% (590 deaths) in the control arm (hazard ratio 0.91, $P = .10$), reported Dr. Le Chevalier, now vice president of GlaxoSmithKline's Oncology Medicine Development Centre (a position not related to his role in the study).

Patients in the chemotherapy arm experienced a significant benefit in disease-free survival at 8 years (hazard ratio 0.88, $P = .02$) and in less local recurrence at 8 years ($P = .002$).

A total of 181 local recurrences were observed in the chemotherapy arm, compared with 230 in the control arm.

Adjuvant chemotherapy also was associated with fewer distant metastases at 8 years.

In all, 338 distant metastases occurred in the chemotherapy arm, compared with 378 in the control arm ($P = .02$). No differences in second malignancies were observed between the two study arms.

Dr. Chevalier observed that chemotherapy continues to protect against death after 5 years, but said the reason for the excess in late mortality is unclear.

He called for more long-term follow-up of patients in adjuvant studies and suggested that data be pooled to identify possible predictive factors.

To that end the IALT investigators assessed 761 patients for expression of ERCC1, a DNA-repair protein, and found that ERCC1 status remained predictive for a survival benefit from adjuvant chemotherapy at 8 years.

Among those who were ERCC1 negative, there was a significant advantage for chemotherapy (hazard ratio 0.76).

Among those who were ERCC1 positive, there was a trend toward favoring observation (hazard ratio 1.20).

Discussant Dr. Pieter E. Postmus, FCCP, noted that this represents a decline in the survival benefit of ERCC1-negative tumors.

In an IALT substudy published in 2006, chemotherapy significantly improved median 5-year overall survival among patients with ERCC1-negative tumors, compared with control patients—47% vs. 39% respectively (hazard ratio .065, $P = .002$) (N. Engl. J. Med. 2006;355:983-91).

For those with ERCC1-positive tumors, the control group fared better in terms of overall survival, though not significantly so—46% vs. 40% respectively (hazard ratio 1.14, $P = .4$).

"The beneficial effect of being ERCC1 negative is apparently disappearing over time," said Dr. Postmus of the department of pulmonary disease at Vrije Universiteit Medisch Centrum, Amsterdam.

"The initial positive effect is due to the low ERCC1 of the tumor; it's unclear why this benefit decreases at longer follow-up," Dr. Postmus added.

As ERCC1 is responsible for DNA repair, he speculated that the possible cause might be more late damage due to chemotherapy, especially in patients with less repair capacity. ■

ACIP Makes Recommendations

Vaccinate • *from page 1*

case of IPD was matched with 10 controls of the same age without IPD. A total of 635 persons with IPD and 6,350 controls was identified, of whom 114 (18%) and 516 (8%), respectively, had asthma. The adjusted odds ratio for IPD among those with asthma, compared with controls, was 2.4, which the authors concluded suggests that asthma is an independent risk factor for IPD (N. Engl. J. Med. 2005;352:2082-90).

Despite data from another case-control study of older veterans with either asthma or COPD which suggested that those with asthma were not at significantly increased risk for IPD-related hospitalizations (J. Gen. Intern. Med. 2007;22:62-7), the committee agreed with the decision made by an ACIP working group prior to the meeting that the bulk of the data suggests that asthma does increase the IPD risk.

Dr. Sandra Fryhofer, acting liaison to ACIP from the American College of Physicians (ACP), agreed.

"Asthma definitely increases the risk of severe pneumococcal infections. The new recommendation includes asthma with other chronic lung diseases. That's a good thing," she said in an interview.

Echoing a point made by several ACIP members during the discussion, she also noted that in adult patients it is often difficult to distinguish between asthma, COPD, and chronic bronchitis.

"I think this is going to make the recommendations easier to follow [and] ensure that the right people get the vaccine," said Dr. Fryhofer, a former ACP president who practices internal medicine in Atlanta.

Also during the same session at the ACIP meeting, the committee voted to clarify language that had been misinterpreted by some providers as suggesting revaccination should take place every 5 years in individuals for whom PPSV23 is recommended.

In fact, routine revaccination is not recommended for most people. A second dose of vaccine—but no more—is recommended at 5 years after the first dose for patients with functional or anatomic asplenia or immunocompromising conditions.

The committee opted not to recommend lowering the age of universal PPSV23 immunization from 65 years and older to 50 years, primarily because such a move would require a change in the schedule for revaccination, for which few data are available.

In addition, the risk of IPD among individuals aged 50-64 years has decreased in recent years because of routine use of the 7-valent pneumococcal conjugate vaccine (PCV7) in infants. The overall IPD rates in adults have dropped 18%-39% since the pre-PCV7 era, Dr. Nuorti said. ■

Congress Reverses Medicare Cuts, Extends 0.5% Increase

BY MARY ELLEN SCHNEIDER
Elsevier Global Medical News

Washington's summertime wrangling paid off for physicians last month as Congress successfully overrode President Bush's veto of legislation to stop a 10.6% cut to Medicare physician payments.

The legislation (H.R. 6331), which originally passed both the House and Senate by veto-proof margins in early July, extends the 0.5% Medicare pay increase in place for the first half of 2008 through the end of the year and gives physicians a 1.1% raise for next year.

THE BILL ALSO PROVIDES INCENTIVES TO ENCOURAGE PHYSICIANS AND OTHER PROVIDERS TO USE ELECTRONIC PRESCRIBING.

Congress financed the pay increases for physicians in part through controversial cuts to Medicare Advantage plans. Officials at America's Health Insurance Plans, which represents the health insurance industry, estimated that the bill will cut nearly $14 billion from the Medicare Advantage plans over the next 5 years. The inclusion of those cuts in the bill slowed its passage in the Senate and caused President Bush to veto the legislation.

The bill also encourages physicians and other providers to use electronic prescribing by providing incentives to those who e-prescribe and imposing penalties on those who do not. In addition, the bill would delay the first round of Medicare's new competitive acquisition program until 2009.

Now that H.R. 6331 is law, Medicare contractors are working to make sure physicians are paid at the correct rate.

However, it may take up to 10 business days for some contractors to begin paying claims at the 0.5% update rates, according to CMS. Once the local contractors start paying claims at the increased rate, they will go back and reprocess any claims paid at the lower amount.

Most claims will be automatically reprocessed, but a few providers may need to contact their local contractor for direction on getting their claims adjusted. For example, physicians who have submitted charges that are lower than the Medicare fee schedule amount will need to contact their local contractor, CMS said. In addition, nonparticipating physicians who submitted unassigned claims at the reduced nonparticipation amount will need to request an adjustment from the carrier. ■

PPI Therapy Fails to Curb Asthma With Asymptomatic GERD

BY NANCY WALSH
Elsevier Global Medical News

TORONTO — Treatment with a proton pump inhibitor did not improve asthma control in patients with poorly controlled asthma and minimal or no symptoms of gastroesophageal reflux, according to results from a large study presented at an international conference of the American Thoracic Society.

Gastroesophageal reflux disease (GERD) is a common problem in patients with asthma, with small studies reporting a prevalence of reflux in 32%-84% of asthmatics. Proton pump inhibitor (PPI) therapy is commonly added to therapy in asthma, adding to the overall cost of treatment, but the effect of suppression of gastric acid on asthma symptoms remains unclear, according to Dr. Mario Castro, FCCP, of Washington University School, St. Louis.

Uncertainty about the role of GERD in asthma derives from observations that approximately half of asthmatics without symptoms of GERD have been demonstrated to have abnormal reflux and about half of asthmatics who have abnormal reflux shown on pH probe studies do not have symptoms of the disease, Dr. Castro said.

"In any case, certainly GERD symptoms can mimic symptoms of asthma, and we wanted to know how to distinguish them and how best to treat them," he said.

Recent guidelines released by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health suggested that, even in the absence of GERD symptoms, consideration should be given to evaluation and possible treatment with PPI for patients with poorly controlled asthma. This was a consensus-based recommendation.

In order to gain additional data to strengthen the recommendation, the Study of Acid Reflux in Asthma (SARA) was undertaken with funding from the NHLBI and conducted by the American Lung Association's asthma clinical research centers, a national 20-center network dedicated to improving asthma care.

"SARA included only patients with minimal or no symptoms of GERD, because we felt that any patient with moderate or severe GERD should, by definition, be receiving a PPI—and, in this trial, there was the possibility that they would receive placebo," Dr. Castro said.

Aside from determining whether PPI therapy could improve asthma symptoms in those patients, SARA also sought to determine whether ambulatory pH probe monitoring could identify patients with asymptomatic GERD who might benefit from suppression of gastric acid.

The study design called for a 2- to 8-week run-in period, during which the patients underwent esophageal pH probe monitoring and, if not contraindicated, methacholine challenge testing. The patients then were randomly assigned to receive esomeprazole, 40 mg/day, along with stable doses of inhaled corticosteroids (equivalent to at least 400 mg fluticasone/day) and long-acting β-agonists if needed.

Poorly controlled asthma was defined as two or more occasions of a 30% or greater decline in peak expiratory flow from baseline, the need for oral prednisone, the requirement for acute intervention such as an emergency department visit, or the need for more than four puffs of rescue medication.

Another investigator, Dr. W. Gerald Teague of the pediatric asthma center at Emory University, Atlanta, described the baseline characteristics of the participating patients.

THE NUMBER OF EPISODES OF DECREASE IN PEAK FLOW WAS 1.7/PERSON PER YEAR IN THE PLACEBO GROUP AND 2.1 IN THE ESOMEPRAZOLE GROUP.

"A total of 412 patients were randomized; but, unfortunately, nature intervened, and the data from 10 patients were lost in Hurricane Katrina," Dr. Teague said. Of the remaining patients, 199 received placebo and 203 received esomeprazole.

Overall, the groups were comparable. Mean age was 42 years, and 50% were white and 38% were black. In the placebo group, 28% were male and 20% were former smokers. In the esomeprazole group, 36% were male and 15% were former smokers.

About half of the patients in both study groups had required the use of rescue medications during the previous year, and the same number had required courses of oral prednisone.

Asthma control also was found to be equivalent in the two groups, with a mean Asthma Control Questionnaire (ACQ) score of 1.9 in the placebo group and 1.8 in the PPI group.

Lung function also was comparable, with a forced expiratory volume in 1 second (FEV_1) at 78% of predicted in the placebo group and 76% of predicted in the esomeprazole group. There were no differences in post-albuterol response, forced vital capacity, or bronchial hyperresponsiveness.

On pH probe testing, 40% of patients in both groups were positive for GERD.

"We were surprised, but when baseline asthma characteristics were analyzed according to whether or not patients were positive for GERD on pH probe testing, there was very little effect," Dr. Teague said.

In both GERD and non-GERD groups, 80% of patients had required rescue medicine, ACQ scores were 1.9, and Asthma Quality of Life scores were 4.6, he reported.

The study results then were summarized by Dr. John G. Mastronarde, who is a pulmonologist at Ohio State University Medical Center, Columbus, and director of the university's asthma center.

"Overall, we saw no treatment effect in either group," Dr. Mastronarde said. The number of episodes of decrease in peak flow was 1.7/person per year in the placebo group and 2.1/person per year in the esomeprazole group. The number of episodes requiring urgent care was 0.7 in the placebo group and 0.6 in the esomeprazole group.

Some studies have suggested that certain subgroups, such as patients with episodes of nocturnal awakening and those with a body mass index greater than 30 kg/m^2, might respond to PPI treatment.

However, those were no different between the placebo and active treatment groups, he said. Lung function as measured on FEV_1, peak flow, and tests of bronchial hyperresponsiveness also showed no effects of treatment, nor did patient-centered outcomes such as ACQ scores, even among patients who had positive pH probe tests, said Dr. Mastronarde.

"In summary, asymptomatic GERD is common in patients with poorly controlled asthma, but PPI therapy with esomeprazole does not improve asthma control or lung function in patients with minimal or absent symptoms of GERD," he said.

"Ambulatory pH probe testing did not seem to identify any subgroups of patients who might benefit from PPI therapy in terms of asthma control," he added.

"We think these results are pretty significant," Dr. Mastronarde added.

"The NIH guidelines suggest that we consider evaluation and treatment in patients with poorly controlled asthma on adequate controllers even without symptoms of GERD, but this study would suggest that PPI therapy has no effect on control and is not indicated," noted Dr. Mastronarde.

"Also, there doesn't seem to be any reason to do pH probe testing on poorly controlled asthmatics, because even if they are positive, it doesn't predict who will respond to PPI treatment." ■

Dr. Susan Harding, FCCP, comments: *This important study verifies the findings found in a previously reported double-blind, placebo-controlled trial examining the effect of esomeprazole 40 mg twice a day for 16 weeks in 770 subjects, on asthma outcomes (Kiljander et al. Am. J. Respir. Crit. Care Med. 2006;173:1091-7). Subjects without GER symptoms or nighttime asthma symptoms had no improvement in PEF. Improvement in PEF was noted in subjects with GER symptoms and nighttime asthma symptoms. This study verifies that treatment of asymptomatic acid GER is not indicated in asthmatics.*

Look Beyond Asthma Symptoms in Assessing Behavior

BY BETSY BATES
Elsevier Global Medical News

HONOLULU — Insight into what's happening at home may help to explain behavior problems and school absenteeism in children with asthma, according to studies presented at the annual meeting of the Pediatric Academic Societies.

Researchers from the University of Rochester (N.Y.) studied sleep-disordered breathing in children with asthma in an attempt to find possible links to problem behavior issues that have previously been reported in this patient population.

The associations were powerful, with serious behavioral problems documented in twice as many asthmatic children with sleep problems as in those with asthma alone, reported Maria Fagnano, health project coordinator for the department of pediatrics at the university.

A second and unrelated study explored school absenteeism among children with asthma and found that parental chronic disease plays a role in how children's health is perceived and in how many school days they miss, regardless of asthma severity.

The New York study enrolled 194 inner-city children aged 4-10 years, with physician-diagnosed asthma, who attended a school-based asthma program.

Parents were administered a 28-item validated questionnaire on behavioral issues (the Behavior Problem Index or BPI) and a 22-item validated questionnaire on sleep patterns, the Sleep-Related Breathing Disorder Subscale.

Most of the children were male (56%); African American (66%) or Hispanic (26%); and on Medicaid (73%). Their average age was 8 years. Prior testing had revealed that almost one-third of their parents suffered from depression.

One-third of the children had sleep scores highly predictive of sleep-disordered breathing, which can range from snoring to sleep apnea, said Ms. Fagnano. Girls and children with high body mass indexes were at higher relative risk of elevated sleep-disordered breathing scores than were other children with asthma in the study.

Nearly the same percentage—32% of children—scored above a 14 on the Behavior Problem Index, a range considered to be indicative of behavior problems serious enough that they might warrant professional intervention.

Twice as many children with high sleep-disordered breathing scores—48%—earned elevated scores on the BPI than did those with normal sleep scores, 24%.

Among problem behavior subscales, independent correlations were found between children with elevated sleep-disordered breathing scores and internalizing behavior problems, externalizing behavior problems, anxious or depressed behavior, headstrong behavior—and, in a separate linear regression analysis, hyperactive behavior.

"A large proportion of urban children with asthma have sleep-disordered breathing, and poor sleep is independently associated with behavior problems," said Ms. Fagnano.

"Screening for sleep-disordered breathing among high-risk populations might help to identify children who could benefit from further interventions," she said.

The second study examined data from 561 parent/child dyads surveyed as part of the nationally representative 2003 National Health Interview Survey, Dr. Ellen A. Lipstein reported at the meeting.

All of the children, aged 5-17 years, had been diagnosed with asthma by a physician, and 39% of their parents reported being diagnosed with a chronic disease such as heart disease, emphysema or asthma, diabetes, or arthritis.

No difference was seen in inhaler use by children of parents with or without chronic disease. When researchers controlled for other factors, including measures of childhood asthma severity, parents with chronic disease were three times less likely to judge their children's health as excellent or very good, and their children missed, on average, 1.3 more days of school during the previous year.

"These findings suggest that parental chronic disease may lead to increased perceptions of child medical vulnerability," said Dr. Lipstein of the Harvard Medical School and the Massachusetts General Hospital center for child and adolescent health policy, both in Boston. "Furthermore, the increased absenteeism suggests that parents with chronic disease not only perceive [greater] child vulnerability, but they act on these perceptions," she said.

Dr. Lipstein said clinicians should be aware that symptom management alone may not "fully address" the reasons for school absenteeism among children with asthma. ■

Central-Line Infections at Zero With New Protocol

BY MARY ELLEN SCHNEIDER
Elsevier Global Medical News

The physicians, nurses, and other clinical staffers at Tacoma (Wash.) General Hospital aren't sweating the new Joint Commission on Accreditation of Healthcare Organizations' requirements on central line–associated bloodstream infections that are scheduled to be phased in throughout 2009.

That's because they have already implemented a central-line protocol that has brought their hospital's infection rate down to virtually zero over the last few years.

"We just had to change our way of thinking on it. Rather than accepting a certain rate of infections, we adopted the position that they should never happen," said Dr. James R. Taylor, FCCP, medical director of the adult intensive care unit at Tacoma General Hospital and the hospital's physician champion on reducing central-line infections.

In 2005, Dr. Taylor began educating physicians and nurses in his ICU about a bundle of measures for reducing central-line infections that he learned about as part of the TICU (Transformation of the ICU) project, a program from the national health care alliance VHA Inc. The staff made an effort to follow the protocol with each central line placed, and success followed, Dr. Taylor said.

Before implementing the central-line protocol, Tacoma General Hospital had an infection rate of about 1.5-2.0 infections per 1,000 central-line days, which was better than the national benchmark set by the Centers for Disease Control and Prevention. Since it implemented the measures in 2005, the hospital's central line–associated infection rate has been even lower. There were no infections in the adult ICU at Tacoma General Hospital for all of 2006 and 2007, said Marcia Patrick, R.N., director of infection prevention and control for MultiCare Health System, which operates Tacoma General Hospital and three other hospitals in the area.

After seeing so much success in the ICU, the hospital generalized the process to the emergency department, the operating rooms, and anywhere else central-line placement was being performed.

The protocol is surprisingly simple, Dr. Taylor said. Its main elements are proper hand hygiene, the use of chlorhexidine-based antiseptic for skin preparation, the use of a sterile drape to cover the whole patient instead of just the area where the line is being placed, the placement of the line in those locations shown to have lower infection rates, and the removal of the catheter as soon as possible.

MARK CELLETTI/MULTICARE HEALTH SYSTEM

The central-line protocol is easy to follow, said Marcia Patrick, R.N., and Dr. Taylor.

The key is to make it easy to follow the measures and difficult to do things the wrong way, Dr. Taylor said. For example, the hospital decided to remove from its line carts anything that might contribute to improper line placement, and to include only those materials that would aid in proper line placement.

Another element of the hospital's success has been empowering nurses to speak up, Dr. Taylor said. Under the protocol, if a physician breaks sterile technique during the line placement, nurses are required to step in and ask the physician to stop and start over. The hospital also created a checklist for nurses to record that all the proper steps in the line placement were performed. ■

Dr. Vera De Palo, FCCP, comments: *A focus on improving patient safety through the implementation of strategies to reduce catheter-related bloodstream infection is being adopted by many health care institutions across the country. Projects like the TICU project of the national health care alliance VHA Inc. and the advocacy and facilitation of quality initiatives by the Institute for Health Care Improvement (IHI) have helped to disseminate these strategies. Large quality collaboratives like the Keystone ICU project in Michigan and the statewide Rhode Island ICU Collaborative have similarly achieved significant reductions in catheter-related bloodstream infection rates. The work of Dr. Taylor and his team at Tacoma General Hospital demonstrates that with education and a focus on safety and quality, these excellent outcomes can be achieved and maintained over time, making it safer for our patients.*

Joint Commission Makes Infection Control Priority

BY MARY ELLEN SCHNEIDER
Elsevier Global Medical News

The Joint Commission has issued new requirements for hospitals in an effort to prevent infections from multidrug-resistant organisms, central line–associated bloodstream infections, and surgical site infections.

The requirements, which are part of the 2009 National Patient Safety Goals for hospitals, include a 1-year phase-in period with full implementation by Jan. 1, 2010.

It is critical that hospitals begin addressing the issue of health care–associated infections and try to keep the problem from worsening, said Dr. Peter Angood, vice president and chief patient safety officer for the Joint Commission. "We're in a bit of a tight spot and we need to work our way out of it," he said.

The new infection control requirements build on an existing National Patient Safety Goal on health care–associated infections that had previously included only requirements for compliance with hand hygiene guidelines and had called on hospitals to manage serious infections as sentinel events. Those requirements will remain in place along with the new elements of the goal.

"Infection control is high on our priority list overall," Dr. Angood said.

Under the new 2009 requirements, hospitals are being asked to begin preparing to prevent infections resulting from multidrug-resistant organisms such as methicillin-resistant *Staphylococcus aureus*, *Clostridium difficile*, vancomycin-resistant enterococci, multidrug-resistant gram-negative bacteria, and other epidemiologically important organisms.

Starting in January 2010, hospitals will need to conduct periodic risk assessments for acquisition and transmission of multidrug-resistant organisms, and educate staff and independent providers about prevention strategies and their roles. Hospitals also will be required to provide education about infection control strategies to patients and families who are infected or colonized with multidrug-resistant organisms.

Hospitals will be required to have a surveillance program up and running by Jan. 1, 2010, that is based on the hospital's risk assessment.

When indicated by the risk assessment, hospitals will need to implement a laboratory-based alert system to identify new patients with multidrug-resistant organisms, and an alert system to identify readmitted or transferred patients who have multidrug-resistant organisms.

There is sufficient evidence to show a clinical benefit from implementing infection control strategies.
DR. MICHOTA

The Joint Commission also has put new requirements in place to prevent central line–associated bloodstream infections and surgical site infections.

As part of the requirements related to central line–associated bloodstream infections, hospitals will be expected to use a catheter checklist and a standardized protocol for central venous catheter insertion and an all-inclusive standardized supply cart or kit for insertion of central venous catheters. The requirements also call for the use of standardized protocols for maximum sterile barrier precautions during insertion of a central venous catheter and when disinfecting catheter hubs and injection ports before accessing the ports.

As part of its effort to prevent surgical site infections, the Joint Commission is requiring hospitals to conduct periodic risk assessments, select surgical site infection measures based on evidence, and evaluate the effectiveness of their prevention efforts. Also, hospital staff will need to measure infection rates for the first 30 days following most procedures and for the first year after procedures involving implantable devices.

The surgical site infection requirements were developed to be in line with well-established guidelines and should help organizations move toward compliance with those guidelines, Dr. Angood said.

All of the new requirements related to health care–associated infections include a 1-year phase-in period, with milestones for planning, development, and testing throughout 2009. Allowing organizations to phase in complex requirements over the course of a year helps them to perform better by achieving concrete goals before full compliance is expected, Dr. Angood said.

Addressing health care–associated infections is a worthy goal, said Dr. Franklin Michota, director of academic affairs for the department of hospital medicine at the Cleveland Clinic. There is sufficient evidence to show a clinical benefit from implementing infection control strategies. "It's not an experiment to see if these things work," he said.

Hospitals are likely to face some up-front costs when implementing the new requirements, Dr. Michota said, especially if they need to put a new educational process in place to prepare staff. For that reason, hospitals may be looking to involve hospitalists, who are already on the payroll, in a variety of activities related to preventing health care–associated infections, he said.

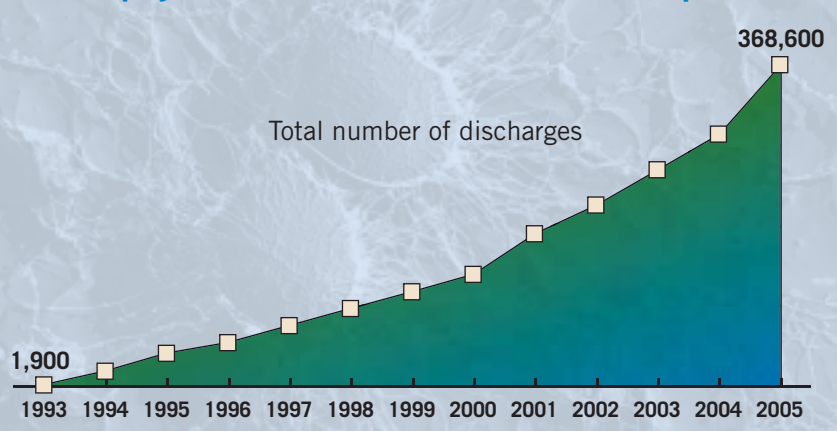
Hospitalists may be involved in developing process improvement plans, tracking requirements, or tracking infections. Those who are not involved on the quality side may be asked to champion changes at the floor level by modeling appropriate hand hygiene or compliance with contact precautions.

The Joint Commission also has added new requirements to the goal for medication reconciliation. Hospitals are advised to provide a complete and reconciled list of the patient's medications directly to the patient and explain the list at the time of discharge. In those settings where medications were used minimally or for a short duration, such as the emergency department, the hospital is required to perform a modified medication reconciliation process. For example, if a short-term course of an antibiotic is prescribed, the patient should be provided with a list containing the medications that the patient will continue using after leaving the hospital.

Also new in 2009 is a requirement to eliminate transfusion errors related to patient misidentification. Before beginning a blood or blood component transfusion, hospital staff must match the patient to the blood during a two-person bedside verification process. In cases where two individuals are not available for this process, a bar code or other automated technology can be used in place of one of the individuals, according to the Joint Commission. ■

DATA WATCH

Steady Growth in Methicillin-Resistant *Staphylococcus aureus* Cases in U.S. Hospitals



Note: Based on data from the Nationwide Inpatient Sample.
Source: Healthcare Cost and Utilization Project

ELSEVIER GLOBAL MEDICAL NEWS

Pulmonary Perspectives

The Role of Genetics in Sarcoidosis

Like many conditions, there is probably a large number of genes that affect the outcome of the disease.

Sarcoidosis has often been associated with a possible genetic predisposition. However, the closer one looks, the association with a genetic predisposition becomes less clear.

To date, the amount of information we have obtained suggests strongly that sarcoidosis is not caused by a single gene or even a small family of genes. Like many conditions, such as asthma, there is probably a large number of different genes that affect the predisposition and clinical outcome of the disease.

For some time, it has been noted that sarcoidosis occurs in different frequencies with different ethnic groups.

Although the original description of the disease was by Hutchins in England (Sharma. *Clin Dermatol* 2007; 25:232), many of the early studies were performed in the Scandinavian countries. Among the Scandinavian investigators was Dr. Sven Lofgren at the Karolinska Institute in Stockholm. As the studies accumulated in Scandinavian countries, it became clear that the incidence of sarcoidosis was higher there than elsewhere in Europe. There also was an increased rate of sarcoidosis noted in women. In a comprehensive study of an area in Sweden by Hillerdal (Hillerdal et al. *Am Rev Respir Dis* 1984; 30:29), the lifetime risk for sarcoidosis in women was 1.3% and almost 1% for men. This rate was confirmed by studies in other Scandinavian countries (Izumi. *Sarcoidosis* 1992; 9:S105).

FOR SARCOIDOSIS, THE GENETIC BACKGROUND SEEMS TO BE ONLY PART OF THE STORY. ENVIRONMENTAL EXPOSURES ALSO APPEAR TO BE QUITE IMPORTANT.

However, these high rates may have been influenced by the availability of national databases allowing for a more complete capture of the population. It also has been observed that the rate of sarcoidosis will increase by one-third if chest radiograph screening for TB is employed in the country.

In the United States, an increased incidence of sarcoidosis in the African-American population has been frequently noted. However, the absolute numbers were harder to obtain. This is, in part, because of the lack of a central database with a collection of information on all patients. For example, several studies of military personnel in the 1950s and 1960s demonstrated an increased incidence of sarcoidosis in African Americans; these studies were composed of, essentially, an all-male population.

Other studies have used death certificates to verify the increased incidence of sarcoidosis in African-Americans; however, most patients with sarcoid did not die from sarcoidosis, and death certificates often will not report past medical problems.

The most comprehensive study looking at sarcoidosis in African-Americans vs Caucasians was from the Henry Ford Healthcare System (Rybicki et al. *Am J Epidemiol* 1997; 145:234). This 5-year study demonstrated an increased frequency in African-American women (lifetime risk, 2.7%) and men (lifetime risk, 2.1%) vs Caucasian women (lifetime risk, 1.0%) and men (lifetime risk, 0.7%). However, this study required enrollment into a health maintenance organization by at least one family member. Others have reported an increased frequency of sarcoidosis in people without access to medical insurance. Therefore, the frequency of the disease may be even higher.

Familial sarcoidosis also has supported genetic predisposition. The reported rate of familial sarcoidosis is around 5%; however, this is influenced by the underlying factor of race. Higher rates of familial sarcoidosis have been reported in Scandinavian, Irish, and African-American populations. Studies of families with sarcoidosis have been used to identify candidate genes for possible sarcoidosis. These candidate genes are then tested in the more divergent population of spontaneous sarcoidosis.

There is compelling evidence to suggest that sarcoidosis is initiated by the presentation of an antigen to the CD-4 T cell, and the resulting complex leads to a Th-1 response. The antigen-presenting cell (either a macrophage or dendritic cell) presents the antigen by the human leukocyte antigen (HLA). There is a large number of genes influencing HLA, so studies of the HLA have been an area of focus for candidate genes in sarcoidosis.

Early studies focused on the HLA class I antigens. It was found by several investigators that HLA-B8 was associated with acute sarcoidosis. This association alone did not explain most cases of sarcoidosis. Recent studies have suggested an interaction between class I and class II genes, which may be more important than the class I antigen alone.

Studies of HLA class II antigens have found several interesting associations (Sato et al. *Am J Respir Cell Mol Biol* 2002; 27:406; Grunewald et al. *Am J Respir Crit Care Med* 2007; 175:40; Maliarik et al. *Am J Respir Crit Care Med* 1998; 158:111). One of the largest studies was performed on patients who participated in the ACCESS (A Case-Control Etiologic Study of Sarcoidosis) study (Rossman et al. *Am J Hum Genet* 2003; 73:720). The study enrolled patients with newly diagnosed sarcoidosis at 10 centers in the United States. The overall makeup of study subjects was half African-American and half Caucasian. The investigators confirmed an increased susceptibility for sarcoidosis in subjects with DRB1*1101 for all patients with sarcoidosis. On the other hand, DRB1*04 was associated with possible protection from sarcoidosis, because it was more frequently found in control subjects than patients with sarcoidosis.

Other genes have been associated with an increased risk for sarcoidosis. In a detailed gene mapping of 63 German families with sarcoidosis, Schurmann et al (*Am J Respir Crit Care Med* 2000; 162:861) found polymorphisms of the butyrophilin-like 2 (*BTNL2*) gene. Studies of American patients by Rybicki et al (*Am J Epideiol* 1997; 145:234) found that BTNL2 was moderately associated with sarcoidosis (odds ratio of 1.6 for heterozygous and 2.8 for homozygous). The association was weaker for African-Americans. The BTNL2 protein is one of a family of genes located in the major histocompatibility complex class II region. Therefore, it is not clear whether *BTNL2* is an important gene itself or simply located near an important gene. Further studies on the linkage will be needed to clarify the role of *BTNL2*.

The prognosis of sarcoidosis also has been found to be influenced by underlying genetic factors. Here, the information is somewhat incomplete because of a lack of a standardized clinical phenotype for patients with sarcoidosis. For example, it is not clear whether a patient with no evidence of active sarcoidosis, but who still has residual scarring, should be considered the same as a patient with no evidence of residual disease. Also, current use of corticosteroid therapy in low doses to maintain a remission of disease may influence the clinical outcome of the patient.

For many investigators, one major exception has been Lofgren syndrome. The presentation of erythema nodosum, periarticular arthritis, and hilar adenopathy has been highly associated with sarcoidosis. It also has been associated with an excellent clinical outcome. Around 80 to 90% of patients with Lofgren syndrome will have complete resolution on chest radiograph and resolution of other manifestations of the disease within a year or two. However, there are some patients with Lofgren syndrome who develop chronic disease that lasts beyond 2 years.

Previously, it has been found that the HLA class II genes *DQB1*0201* and *DRB1*03010* were associated with Lofgren syndrome for various ethnic groups. Subsequently, Grunewald and Eklund (*Am J Respir Crit Care Med* 2007; 175:40) established the clinical outcome of patients presenting with hilar adenopathy and periarticular arthritis and/or erythema nodosum. They determined that men were more likely to present with arthritis alone, while women were more likely to have erythema nodosum. However, the clinical outcome for men and women was the same. They found that while some of their patients did quite well, they also found a group of patients who had chronic disease. They found that 70% of their study population was DQB1*0201/DRB1*0301-positive and 103 of the 104 patients had resolution within 2 years. Forty patients were DQB1*0201/DRB1*0301-negative, and only 22 cases resolved within 2 years. This supports the idea of performing HLA phenotyping to determine patient prognosis. While this appears to be quite useful in Swedish patients, there is incomplete information about its applicability in other populations.

On the other end of the extreme are patients with chronic disease. HLA-DRB3*0101 has been associated with chronic disease in the Caucasian population. Several groups have noted that the HLA-DRb1*15-positive patients are more likely to have chronic disease. Dr. Drent's group (Voorter et al. *Hum Immunol* 2005; 66:826) found that, in a Dutch population, DQB1*0602/DRB1*150101 was associated with chronic disease and fibrotic changes on chest radiograph.

Another way to look for genetic effect on disease outcome is to examine familial sarcoidosis. In a detailed study of 203 African-American families with two or more members with sarcoidosis, evaluation was performed on 509 patients with sarcoidosis. Judson et al (*Chest* 2006; 130:855) reported a similarity between different family members and different manifestations of the disease. Patients were likely to share eye and skin problems more frequently than the population with spontaneous sarcoidosis.

Interestingly, many of the manifestations of sarcoidosis were not concordant with the familial cases. Clinical outcome also was likely to be different between family members. This lack of close association suggests that it is not just genetics or a single gene that influences the manifestations of sarcoidosis, at least in the African-American population.

For sarcoidosis, the genetic background seems to be only part of the story. Environmental exposures also appear to be quite important. It is not clear if there is one or more than one environmental agent. Several recent reports have associated sarcoidosis with the World Trade Center disaster, *Propionibacter acnes*, and mycobacteria (Izbicki et al. *Chest* 2007; 131:1414; Eishi et al. *J Clin Microbiol* 2002; 40:198; Song at al. *J Exp Med* 2005; 201:755). Future research will need to combine these factors together as we try to unravel the enigma of sarcoidosis. ■

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Editor, *Pulmonary Perspectives*

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NEWS FROM THE COLLEGE

EDUCATION INSIGHTS

How Much Value Do You REALLY Place on Your CME?

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

ACCP members expect us to offer quality continuing medical education (CME) and may take for granted our ability to provide it. As a clinical and educational society, members often assume that CME occurs automatically with many ACCP meetings and products, but have you really thought about what CME means and the value you place upon it? Is it really about medical education, or do you value CME just to get the hours to fulfill your requirements for your medical license, your hospital privileges, or your maintenance of certification?

A recent article (*J Contin Educ Health Prof* 2008; 28:95) concluded the following about CME and those who participate in it:

1. State medical boards should require valid and reliable assessment of physicians' learning needs.
2. CME planners should create learning activities on the basis of the assessed practice needs of physicians.
3. CME planners and policy makers should raise research in CME and physician assessment to a national priority.

In addition to questioning the goals and nature of CME, there are recurring questions about the impact of pharmaceutical industry support and potential conflicts of interest of physician faculty and participants. There are ongoing discussions by government and professional regulatory agencies about the role and nature of industry funding of medical education at the undergraduate and postgraduate levels and the safeguards that are in place, as well as the need to avoid improper influence on content. A number of proposals and recommendations has come from various quarters. The US Senate Finance Committee recommended that policy makers and regulators change their monitoring system. The American Medical Association's (AMA) Council on Ethics and Judicial Affairs (CEJA) and the Macy Foundation recommended elimination of all commercial support in CME. The Association of American Medical Colleges has proposed and received approval to put stricter policies in place by July 2009 that manage commercial support within medical education and conflict of interest of faculty. Thus far, the AMA's CEJA report was referred back to the committee for further study. However, the Accreditation Council for Continuing Medical Education (ACCME) has recently implemented new policy changes with another proposal of additional policies open for public comment until August 11, 2008.

For more information about any or all of these recommendations and proposals, I encourage you to visit the following Web sites:

- US Senate Finance Committee http://hcrenewal.blogspot.com/2007/05/senate-finance-committee-report-on.html
- Josiah Macy, Jr. Foundation Report www.josiahmacyfoundation.org/
- AAMC, www.aamc.org/research/coi/
- AMA/CEJA, www.policymed.com/2008/06/ama-ceja----bac.html
- ACCME, www.accme.org/index.cfm/fa/news.detail/News/.cfm/news_id/c7b2d7ee-854d-4440-9b87-265746af2495.cfm

What can you as an ACCP member do in response? First, I suggest that you consider the value that ACCP education has in your professional activities, and demand that we provide the highest-quality CME programs and support them. Starting at CHEST 2007, we have enhanced value by specifying and enriching the learning categories in all of our activities. Applying these learning categories to each ACCP CME certificate reflects the diversity and effectiveness of learning, along with the hours in which you participated in ACCP medical education programs.

We have responded to your clinical needs by offering areas of study that you asked for, provided direct and personal feedback to participants in ACCP simulation center activities, and, also, placed firewalls to manage commercial support. All of these efforts meet and exceed the requirements of ACCME.

Education is at the core of the ACCP mission, and, perhaps, the most important aspect of our value to our members. Therefore, the ACCP must not resist the coming changes in medical education; rather, we must embrace them and lead. With the leadership and support of the College, I believe that others will look to ACCP as the thought leaders who created value that physician learners respect and use in their daily clinical practices.

I welcome your responses, and invite you to send them to me at edellert@chestnet.org, so I can share them with the ACCP Education Committee and the leadership of the College. ■

The CHEST Foundation's Making a Difference Awards Dinner

Saturday, October 25, 2008

The CHEST Foundation's 10th Annual Making a Difference Awards Dinner will honor ACCP members for their award winning pro bono service projects from around the world.

There will also be special tribute to Forrest M. Bird, MD, PhD, ScD. Dr. Bird is the inventor of the world's first mass-produced medical respirator and the "BABY-Bird," which significantly reduced breathing-related infant mortality rates.

Additionally, the ACCP Industry Advisory Council will confer their annual award to this year's Community Outreach Event elementary school.

Please join your ACCP colleagues and friends on Saturday, October 25, 2008, at the Philadelphia Marriott Downtown, 1201 Market Street, Philadelphia, PA, for an open reception from 7:00 PM to 7:45 PM, and the dinner and ceremonies from 8:00 PM to 10:30 PM.

Due to the close proximity of the Philadelphia Marriott Downtown hotel to other CHEST meeting hotels, transportation will not be provided this year.

THE CHEST FOUNDATION℠

The CHEST Foundation's 10th Annual Making a Difference Awards Dinner Sponsors, to date, are: AstraZeneca, LP; Boehringer Ingelheim Pharmaceuticals, Inc.; and Merck & Co., Inc.

Making a Difference Society members at the $1,000 level are entitled to two complimentary tickets. Annual donors at the $500 level are entitled to one complimentary ticket.

To register online, go to www.chestfoundation.org. To obtain more information, contact Teri Ruiz at truiz@chestnet.org, or by phone at (847) 498-8308. ■

NEWS FROM THE COLLEGE

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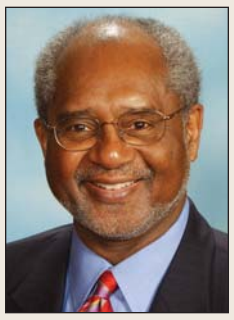

BY DR. ALVIN V. THOMAS, JR., FCCP

PRESIDENT'S REPORT

ACCP Guidelines Not To Be Missed

The eighth edition of Antithrombotic and Thrombolytic Therapy: ACCP Evidence-Based Clinical Practice Guidelines was released in June (*CHEST* 2008; 133[suppl]:67S-968S). Over the years, it has proven to be the gold standard, evidence-based clinical practice guidelines on the topic. This publication is 968 pages long and weighs 2.5 pounds! I congratulate the editors, writing panel, and the ACCP Health and Science Policy Committee that contributed to this essential and monumental effort. Also, believe it or not, planning for the 9th edition of the guidelines is well underway!

The guidelines have become even more important because prevention of deep vein thrombosis has become a national (United States) quality indicator for hospitals.

Two important chapters in the supplement are the guidelines on treatment and prevention of venous thromboembolism (VTE). I attended the First Annual Canadian Respiratory Conference in Montreal (June 19-21, 2008) and was moderator of a presentation on the ACCP guidelines for management and prevention of VTE, given by one of the guideline authors—Dr. William H. Geerts, FCCP. Dr. Geerts gave a wonderful summary of the management and prevention guidelines. He listed some key changes in the VTE management guidelines since the last guidelines in 2004. They are as follows:

- The management guidelines for DVT and pulmonary embolism (PE) are virtually the same;
- The addition of fondaparinux and fixed-dose unmonitored subcutaneous heparin (unfractionated heparin) as acute treatment;
- For PE, subcutaneous, low-molecular-weight heparin is recommended over IV heparin for nonmassive PE;
- There is now more positive consideration of catheter-directed thrombus reduction for DVT and PE;
- The guidelines recommend against inferior vena cava filter use unless anticoagulation is contraindicated; and
- There are stronger recommendations for indefinite anticoagulation in unprovoked VTE.

Though some of the above changes are quite interesting and may be controversial, the evidence clearly supports the recommendations. I hope you find the 8th edition of these guidelines to be thought-provoking and an essential guide to the prevention and treatment of these most important and vexing conditions. ■

PCCU Lessons for August

Management of the Patient With Traumatic Brain Injury
By Dr. David P. Ciceri

Microangiopathic Hemolytic Anemia in the Critically Ill: Thrombotic Thrombocytopenic Purpura-Hemolytic Uremic Syndrome
By Dr. Alan Lichtin

AMERICAN COLLEGE OF CHEST PHYSICIANS®

NEWS FROM THE COLLEGE

Philadelphia—Where History Was Made

During the blistering summer of 1776, 56 courageous men gathered at the Pennsylvania State House to declare independence from England. Eleven years later, representatives from 12 states gathered to shape the US Constitution, finally creating one unified nation. It all happened in Philadelphia.

Known as the birthplace of our nation, Philadelphia is a mecca for US history. Here, you can retrace the steps of Benjamin Franklin, catch a glimpse of the Liberty Bell, or tour a former stop on the Underground Railroad. These and other celebrated landmarks will give you a brief but fascinating history lesson, sharing how our nation's past shaped its future.

Step back in time to see, hear, and experience the early years of the United States of America by visiting the following sites:

▶ **Independence Hall:** Located in Independence National Historic Park, Independence Hall is the birthplace of both the Declaration of Independence and the Constitution. Initially known as the Pennsylvania State House, Independence Hall also is the site where George Washington was appointed commander in chief of the Continental Army and where the American flag was adopted.

▶ **Liberty Bell:** Internationally known symbol of freedom, the Liberty Bell is located just steps away from Independence Hall. Cast in London in 1753, the bell cracked upon its first use. The bell was recast twice but cracked once more in 1846 after it rang for a George Washington birthday celebration. It has not been rung since.

▶ **Congress Hall:** Home of the US Congress from 1790 to 1800, Congress Hall showcases the House of Representatives on the first floor (Lower House) and the recently restored US Senate on the second floor.

▶ **Christ Church and Burial Ground:** Christ Church (Protestant Episcopal) was established in 1695, but the current building dates to 1744. George Washington and John Adams attended services here, while Benjamin and Deborah Franklin and Betsy Ross were parishioners. Located three blocks from the church is the historical burial ground, the final resting place for some of the most prominent US leaders, including Benjamin Franklin and four other signers of the Declaration of Independence.

▶ **Franklin Court:** Franklin Court is the site of Benjamin Franklin's house. The grounds feature a "ghost house," a skeletal structure outlining the shape and dimensions of Franklin's home. Also on the grounds is Franklin's Print Shop, a replica of the 18th century print shop and printing press used by Benjamin Franklin to print the *Pennsylvania Gazette*, the most successful newspaper of its time.

Join us at CHEST 2008 in Philadelphia, the place where history was made. Learn more about Philadelphia's history at www.PhiladelphiaUSA.travel/accp. Learn more about CHEST 2008 at www.chestnet.org. ■

CHEST 2008

DATES TO KNOW

Registration
August 29: Early registration discount ends
October 7: Last day for registration refunds
(Refunds are not available for simulation registrations or guest fees.)
October 8-23: Online registration only
October 24-30: On-site registration available

Housing
September 26: Attendee reservation cutoff
September 5: Exhibitor reservation cutoff

Guest Tours
October 9: Preregistration closes

Philadelphia
October 25-30, 2008

NEWS FROM THE COLLEGE

AMERICAN COLLEGE OF CHEST PHYSICIANS

CRITICAL CARE COMMENTARY

ICU Staffing: What Is the Optimal Mix of Providers?

Over the last decade, ICUs with intensivists (defined as "individuals trained in the subspecialty of critical care, regardless of their primary training") and other professionals skilled in the delivery of critical care services have received considerable attention.

This attention is the result of multiple forces that vary across institutions but include the following goals: (1) improving the quality of care delivered; (2) optimizing the efficiency with which ICU care is provided; and (3) using quality and/or other performance measures in marketing or contracting for services.

Several studies have suggested that mortality can be reduced and length of stay shortened when intensivists provide care for patients in an ICU (Pronovost et al. *JAMA* 2002; 288: 2151; and Young et al. *Effective Clinical Practice* 2000; 6:284).

These studies were seminal in forming the Leapfrog Group, a consortium of large corporations providing healthcare benefits to their employees, organizations of health-care purchasers, and liaisons from several governmental organizations, including the Centers for Medicare and Medicaid Services and the Department of Defense.

The Leapfrog Group promulgated a set of four practices to improve the quality of inpatient care, defined by low mortality, high safety and high patient satisfaction, and expecting that high quality care is also cost-efficient.

One of these practices is the Leapfrog ICU physician staffing (IPS) standard (www.leapfroggroup.org). To meet the IPS standard, the ICU must be managed by an intensivist, an intensivist must be present during daytime hours, and must provide care exclusively in the ICU. Acknowledging the scarceness and cost of 24/7 physician staffing, the Leapfrog IPS standard accepts nonphysician or nonintensivist physician ICU coverage when they have been FCCS-certified (Fundamentals of Critical Care Support—www.sccm.org) and have intensivist backup readily available during night hours.

Indeed, if the intensivist is not present or on-site via telemedicine, they must answer pages within 5 minutes at least 95% of the time and arrange for a physician (or FCCS-certified physician extender) to reach the patient within 5 minutes (www.leapfroggroup.org/media/file/Leapfrog-ICU Physician Staffing Fact Sheet.pdf).

In the 2006 Leapfrog survey, fewer than 30% of responding hospitals fully met the IPS standard. Of the hospitals not meeting the IPS standard, cost (61%) and the shortage of intensivists (36%) were cited as moderately to extremely important barriers to meeting the standard (Pronovost et al. *Crit Care Med* 2007; 35:2256).

The shortage of intensivists was the focus of a recent Report to Congress by the Department of Health and Human Services (Health Resources and Services Administration. Report to Congress: The critical care workforce: a study of the supply and demand for critical care physicians. 2006. Senate Report 108-81). In this extensive analysis of critical care manpower, it was estimated that intensivists cared for less than one-third of patients hospitalized in ICUs in the United States, and that if this were increased to only one-half, there would be a shortfall of an additional 25% from the projected available supply of critical care physicians.

Many centers are exploring the use of telemedicine, especially at night, to increase the availability of intensivist services. While the start-up costs can be high, remotely linked intensivist services have been shown to improve outcomes in some settings (Breslow et al. *Crit Care Med* 2004; 32:31).

The ability to generalize these findings is not yet clear, and the relative merits of this approach as opposed to other staffing methods known also are not clear. While intensivists bill for services rendered, third-party reimbursement for these services often does not cover their full costs, especially when services are provided at night or when services are mandated throughout an ICU whose census or level of intensity is variable.

The institutions themselves usually subsidize these additional costs. In the 2006 Leapfrog survey, over 80% of the hospitals surveyed provided some financial support for intensivists, and 25% of those hospitals meeting the IPS standard provided full support for intensivists (Pronovost et al. *Crit Care Med* 2007; 35:2256).

In academic centers, house staff coverage of ICUs is an option for meeting the IPS standard. Due to ACGME duty hour and curricular demands, and a reduction in the number of house staff in many centers, the supply of available house staff is decreasing while the demand for ICU coverage is increasing. Acute Care Nurse Practitioners (ACNPs) or Physician Assistants (PAs), as physician extenders, can provide first-line ICU care in off-hours at a lower cost than intensivist coverage. In 1997, fewer than 10% of ICUs employed ACNPs or PAs (Brilli et al. *Crit Care Med* 2001; 29: 2007).

Recent reports have examined both the utility and cost-effectiveness of ACNPs and PAs on the critical care management team (Caserta et al. *J Neurol Sci* 2007; 261:167; and Bloomfield et al. *Mayo Clin Proc* 2006; 81: 1457). ACNPs were initially developed within pediatric programs to extend coverage in the outpatient arena. Their role in intensive care was initially within neonatal ICUs (NICUs), and this experience populates much of the small body of data regarding outcomes of care provided by ACNPs. In a controlled trial of patient care in a NICU by ACNPs vs pediatric residents, when supervised by neonatologists, outcomes (short and long-term), costs of care, and patient satisfaction did not differ significantly. Similar results can be obtained in adult subspecialty ICUs, as well (Caserta et al. *J Neurol Sci* 2007; 261:167). The Mayo Clinic, however, found 24/7 Leapfrog-compliant coverage by ACNPs or PAs to be more expensive than house staff coverage, but costs varied widely across the three sites studied due to the numbers of available house staff. The cost of house staff did not take into account the inefficiency of house staff rotation and orientation to the ICUs or the costs related to the role of attending physicians in the educational program of house staff, but neither did it account for Medicare direct and indirect medical education reimbursements.

Critical Care Institute
American College of Chest Physicians

A recent study examined the impact of providing 24/7 continuous, rather than on-demand, attending coverage in a single medical ICU that was staffed by residents and fellows at all times (Gajic et al. *Crit Care Med* 2008; 36:36). Continuous, rather than on-demand attending coverage, was associated with a small, statistically insignificant reduction in readmission to the ICU, with improved patient satisfaction and a modest increase in adherence to recommended processes of care (to which there was already very high adherence). There were no changes seen in length of stay or mortality. The marginal benefit of continuous intensivist coverage requires additional study in different settings and with various models of care.

A plan for optimizing ICU staffing should also take into account the level of experience of the nursing and ancillary staff during day and night shifts. Studies cited by the Agency for Healthcare Research and Quality (www.ahrq.gov) demonstrate that a more experienced staff, especially at night, improved patient outcomes and lowered overall costs of care. Having a more experienced staff during off hours, however, increases the ICU's budget for salaries.

Each facility and their specific needs should dictate the model for care teams and integration of house staff, attending physicians, and ACNPs/PAs. In situations where house staff is either not available or not present in sufficient numbers to provide coverage, ACNPs or PAs appear to provide an acceptable and cost-effective staffing model. House staff and ACNP/PA staffing models are not mutually exclusive, and both can be integrated into models that provide 24/7 bedside coverage for critically ill patients. Indeed, ACNPs/PAs assigned to specific ICUs would likely adhere more strictly to guidelines and recommended practices than house staff who rotate across multiple hospital services.

Areas that require discussion and resolution of potential conflict include the following: (1) the institutional commitment (both administrative, financial, and cultural) to the ACNP/PA program; (2) implementation of a comprehensive program with a defined ACNP/PA coordinator (rather than hiring a single practitioner); and (3) orientation and education for attending staff, house staff, bedside nurses, and ACNPs/PAs that stresses the complementary roles of house staff and ACNPs/PAs and a team-based approach to care (Jastremski. *Semin Respir Crit Care Med* 2001; 22:89).

Recently, Levy and colleagues (*Ann Intern Med* 2008; 148;801) reported that intensivist care resulted in increased costs and mortality. However, the level of intensivist involvement (consultation, co-management, full management) and intensivist presence in the ICU and responsibility for unit management (all components of the Leapfrog IPS) were not reported.

While the bulk of evidence indicates that high intensity staffing (*eg*, Leapfrog IPS) is associated with improved outcomes and lower global costs, studies examining the impact on cost and quality of care of these differing practice models are urgently needed.

Until the various practice permutations have been comprehensively analyzed, development of an optimal, institution-specific staffing model remains as much an art as it is a science. ■

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AMERICAN COLLEGE OF CHEST PHYSICIANS

NEWS FROM THE COLLEGE

NETWORKS

Updates on New TB Tests, IPFnet, and Sleepy Workers

Chest Infections

Recently, two T-cell based interferon-gamma release assays (IGRAs) for the diagnosis of TB infection have been licensed for commercial distribution: the QuantiFERON® -TB Gold (Cellestis, Victoria, Australia) and the T-SPOT.TB® (Oxford Immunotec, Oxford, UK). IGRAs have several advantages over the tuberculin skin test (TST), mainly related to ease of test administration and patient convenience. An additional advantage is that IGRAs do not cross-react with antigens in the Bacille Calmette-Guerin (BCG) vaccine.

How should these new tests be used? The US Centers for Disease Control and Prevention recommends that IGRAs may be used in place of the TST in "all circumstances" where the TST is currently being used, including the evaluation of suspected TB disease and screening for latent TB infection (LTBI). Other groups have issued more conservative guidelines. The UK National Institute for Clinical Excellence has suggested screening most patients initially with the TST and using IGRA as a second test if the TST is positive. Both the IGRA and TST may be negative in the setting of the individual patient with active TB. Similarly, neither the IGRA nor the TST can be used to distinguish active from latent TB.

What is the role of IGRAs for large scale screening programs? We feel the IGRA may have a role in screening for LTBI in health-care workers, particularly those who have received prior BCG vaccination. In July 2007, the Cleveland Clinic began testing all new employees at our institution with IGRA in lieu of the TST. This led to a number of laboratory and financial challenges related to large-scale implementation of a new test (over 2,000 tests in the first 9 months). We also observed an 8% prevalence of indeterminate IGRA results that necessitated additional protocols for weekly tracking of indeterminate results.

A number of questions regarding large-scale IGRA testing remains, including the reproducibility of T-cell responses over time and the appropriate threshold (cutoff) to define an IGRA conversion. Successful implementation of IGRA requires education of all stakeholders involved and flexibility, as new studies evaluate the feasibility and value of these tests.

Dr. Carlos M. Isada, FCCP
Steering Committee Member;
and Dr. Steven M. Gordon

Interstitial and Diffuse Lung Disease

Last year, we reported on the development of the IPFnet projects sponsored by the NIH. We would like to take an opportunity to update you on the progress involved in this very important clinical research effort.

The IPFnet is charged with the development and implementation of clinical trials. The steering committee consists of 11 centers (University of Chicago, University of California San Francisco, University of California Los Angeles, University of Washington, Weil Cornell, Mayo University, University of Michigan, Vanderbilt University, Tulane University/University of Alabama Birmingham, Emory University, and National Jewish Medical Center in Denver) and now several additional centers (St. Lukes - St Louis, Cleveland Clinic, University of South Carolina, University of Pennsylvania, Highland Hospital-University of Rochester, Duke University, University of Miami, Yale University, and University of Utah) are being added to more comprehensively provide an opportunity for subjects to enroll.

Two trials have been developed, and a third is being designed. The IPFnet hopes that these efforts will improve the care of these difficult-to-treat patients. The IPFnet is currently enrolling subjects into the STEP (sildenafil trial of exercise performance in idiopathic pulmonary fibrosis) with great success. As its name implies, this study is focused on improving 6-min walk testing with sildenafil. The implications for an improved quality of life in patients with severe disease are clear. This category of patients has not been and will likely not be involved in pharmaceutical trials.

The Panther protocol, looking at prednisone, azathioprine and N-acetylcysteine, is fully approved and awaiting completion of study drug production. The IPFnet hopes to answer the question once and for all regarding the merits of what has been described as the "standard of care" with this placebo-controlled trial. This critical question can only be answered with enthusiastic enrollment on everyone's part.

The IPFnet is developing a third protocol with more details to come. We hope that pulmonary practitioners will take advantage of the IPFnet and the protocols to offer treatment options to these patients. Only with enrollment in such efforts will effective therapies be found.

Dr. Imre Noth, FCCP, NetWork Vice-Chair

Sleep Medicine

As part of its 11th annual Sleep Awareness Week, the National Sleep Foundation published its "Sleep in America" poll in March 2008. (Read about the results of the ACCP's "ECHO" Poll on page 19 of the May 2008 *CHEST Physician* at www.chestnet.org/physician/0508.pdf.)

One thousand Americans, age 18 years and older and working at least 30 hours per week, were interviewed by telephone for this year's poll, which focused on American workers.

Those surveyed work, on average, nearly 45 hours weekly. Workdays average 9 hours and 28 minutes, and 13% of the respondents work greater than or equal to 60 hours weekly. American workers, on average, sleep only 6 hours and 40 minutes on workdays. On non-workdays, they sleep about 7 hours and 25 minutes. One in six sleeps less than 6 hours nightly.

Nearly half awaken not refreshed at least a few days each month. In > 40%, sleep problems occur nightly or almost nightly, and 5% never get a good night's sleep! Nearly half of the respondents nap at least twice per month, for nearly 1 hour per nap; 10% of workers have napped at work. Of those interviewed, 32% reported that they drove while drowsy at least once a month in the past year, while 36% of drivers have nodded off or fallen asleep while driving.

Eleven percent report difficulty in falling asleep, staying asleep, waking up too early, and that sleepiness interferes with their daytime functioning. Sixty percent of those with insomnia drive drowsy! Similar impairments were experienced among the 11% found to satisfy clinical criteria for restless legs syndrome (RLS) and the 14% at risk for obstructive sleep apnea (OSA).

Despite meeting clinical criteria for insomnia, OSA, or RLS, respondents are underdiagnosed by their physicians. While 14% meet criteria for being at risk for OSA, only 9% have been diagnosed, and only about one-third are being treated.

Modern economic pressures and modern technology have caused the workplace to encroach more on free time at the expense of sleep. Poor sleep, short sleep, and long hours contribute to multiple effects on the quality of work, including injuries to themselves or others at work.

Dr. Steven M. Brown, FCCP
NetWork Member

NEWS FROM THE COLLEGE

AMERICAN COLLEGE OF CHEST PHYSICIANS

ACCP Congratulates Three for Achievements

▶ **Dr. Mary Anne McCaffree, FCCP,** has been elected to the AMA Board of Trustees.

Currently, Dr. McCaffree is the chair of the Council on Science and Public Health, a prominent advisory committee to the AMA, and a member of the Pediatric Section Council of the AMA. Dr. McCaffree is a professor of pediatrics at the University of Oklahoma Health Sciences Center in Oklahoma City, and she is recognized as an experienced researcher and leader.

She is committed to ensuring that all patients receive quality health care and previously led the state of Oklahoma to expand care for sick newborns, working within the medical community groups to implement changes to improve care for infants and children. Dr. McCaffree chaired the ACCP Women's Health Network and is actively involved in the outreach programs for school children, focusing on prevention of tobacco use.

▶ **Dr. Richard S. Irwin, FCCP,** and **Cynthia French, NP, MS,** have been awarded the MDA Lou Gehrig Humanitarian Award by the Muscular Dystrophy Association for their work providing interdisciplinary and patient-focused care for more than 25 years to people with amyotrophic lateral sclerosis (ALS).

Dr. Irwin and Ms. French, who began treating patients with ALS for pulmonary-related complications in the Lung and Allergy Center at UMass Memorial Medical Center almost 25 years ago, noticed that most of their patients had difficulty managing appointments with multiple doctors at multiple locations. They worked to foster an interdisciplinary approach to treatment with services centralized in one location.

The award was presented to Irwin and French by Dr. David Chad, director of the MDA/ALS Center at UMass Memorial Medical Center, and winner of last year's MDA Lou Gehrig Humanitarian Award. Dr. Irwin is the Editor in Chief of the journal *CHEST*, and Ms. French is the Assistant Editor.

The ACCP congratulates you on these great achievements! ■

Journal Citation Report: *CHEST* Impact Factor Increases

In June, the Journal Citation Report statistics (including impact factor) for 2007 were released by the Institute of Scientific Information (ISI). *CHEST* fared well, with its impact factor rising from 3.924 to 4.143—its highest impact factor ever. *CHEST*'s impact factor ranking remains 6th out of 34 respiratory journals.

CHEST also scored highly in the following Journal Citation Report categories:

▶ Total Citations: 35,675 (ranked 2nd of 34 journals)
▶ Number of Articles: 560 (ranked 2nd of 34 journals)
▶ Immediacy Index: 0.918 (ranked 5th of 34 journals)
▶ Cited Half-Life: 7.0 (ranked 10th of 34 journals) ■

This Month in *CHEST*: Editor's Picks

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

▶ **Long-term Use of Sildenafil in Inoperable Chronic Thromboembolic Pulmonary Hypertension.**
By Dr. J. Suntharalingam, et al.

▶ **Comparison of a Combination of Tiotropium Plus Formoterol to Salmeterol Plus Fluticasone in Moderate COPD.**
By Dr. K. F. Rabe, et al.

▶ **Predictors of 30-Day Mortality and Hospital Costs in Patients With Ventilator-Associated Pneumonia Attributed to Potentially Antibiotic-Resistant Gram-Negative Bacteria.**
By Dr. K. E. Kollef, et al.

▶ **Impact of Cough Across Different Chronic Respiratory Diseases: Comparison of Two Cough-Specific, Health-Related Quality of Life Questionnaires.**
By Dr. L. Polley, et al.

▶ **Role of the Ethics Committee: Helping To Address Value Conflicts or Uncertainties.**
By Dr. M. P. Aulisio, and Dr. R. M. Arnold

▶ **Illnesses at High Altitude.**
By Dr. R. B. Schoene

www.chestjournal.org

Proposed Staging System Aids Lung Cancer Patients

BY DOUG BRUNK
Elsevier Global Medical News

SAN DIEGO — Application of a staging system proposed by the International Association for the Study of Lung Cancer resulted in a statistically significant interstage shift in 17% of patients, results from a large single-center study demonstrated.

In addition, the stage shift may alter disease management in 12% of patients, Dr. Edmund S. Kassis reported at the annual meeting of the American Association for Thoracic Surgery.

"We conclude that the IASLC system is more effective than the UICC-6 [Union Internationale Contre le Cancer–sixth edition] at differentiating operable patients based on stage," said Dr. Kassis of the department of thoracic and cardiovascular surgery at the University of Texas M.D. Anderson Cancer Center, Houston.

"Use of this system will help to identify those patients at higher risk for recurrence and will facilitate adjuvant treatment decisions and research," he said.

Adopted in 1997, the UICC-6 staging system has remained unrevised despite advances in imaging and statistical methodology. The IASLC staging committee recently proposed changes to the T, M, and overall stage groupings. The committee's proposal was recently submitted to the UICC and a decision is expected to be rendered in 2009.

The proposed changes to the overall stage groupings could lead to stage changes that might alter treatment, Dr. Kassis said. These include node negative tumors greater than 5 cm (J. Thorac. Oncol. 2007;2:593-602). "This will change the stage from IB where surgery alone is the current treatment to IIA or IIB where adjuvant therapy is frequently recommended," he explained. "Also, tumors greater than 7 cm with N1 disease will be restaged from stage IIB to stage IIIA."

Primary lobe satellite tumors will be reclassified as IIB or IIIA depending on the presence or absence of nodal disease. Satellite nodules in nonprimary lobe will also be reclassified with stage depending on the presence of nodal disease.

To determine the effects of applying the IASLC staging system on patients' stage and to directly compare the IASLC and UICC-6 systems' effectiveness at stratifying operable patients, Dr. Kassis and his associates studied 1,154 patients who underwent complete surgical resection for non–small cell lung cancer at M.D. Anderson Cancer Center between 1998 and 2006. Pre- or postoperative chemotherapy or radiation therapy were not exclusion criteria.

Pathologic data for each patient were entered into a prospectively collected database and the T, M, and overall stage groupings of both the UICC-6 and IASLC systems were applied to each patient.

The mean age of the patients was 66 years and 53% were male. Most patients had either adenocarcinoma (57%) or squamous cell disease (34%), and the majority (82%) underwent lobectomy or bilobectomy.

Dr. Kassis reported that application of the IASLC system resulted in a statistically significant shift of patients between stages, with a total of 202 (17%) patients changing stage. Of these 202 patients, 73 were upstaged and 129 were downstaged.

Of the 73 patients who were upstaged, 63 stage IB patients were upstaged to either stage IIA or IIB, and 10 stage IIB patients were upstaged to IIIA.

Of the 129 patients who were downstaged, 67 IIB patients were downstaged to IIA. Of 59 IIIB patients, 8 were downstaged to IIB and 51 were downstaged to IIIA. Of the three stage IV patients, two were downstaged to IIIA and one was downstaged to IIIB.

Dr. Kassis said the IASLC system potentially altered management in 134 (12%) of patients. No patients were upstaged to an unresectable stage, 63 patients were upstaged to a stage where adjuvant chemotherapy is frequently offered, and 61 patients were downstaged from IIIB or IV to a stage often offered surgical resection.

The researchers were concerned that shifting patients from UICC-6 IIIB/IV into IASLC IIIA would compromise 5-year survival. However, the 5-year survival for IASLC IIIA and UICC-6 IIIA were comparable at 39% and 37%, respectively.

Dr. Kassis had no conflicts of interest. ■

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Severe Sleep Apnea Raised All-Cause Mortality in 14-Year Study

BY HEIDI SPLETE
Elsevier Global Medical News

BALTIMORE — Moderate to severe sleep apnea significantly increased the risk of all-cause mortality, according to 14 years of follow-up data from a large community sample.

"Sleep apnea is a disease of public health significance," said Nathaniel Marshall, Ph.D., of the University of Sydney, who presented results from the Busselton Health Study at the annual meeting of the Associated Professional Sleep Societies.

Previous studies have suggested that obstructive sleep apnea (OSA) increases the risk of death from cardiovascular disease, Dr. Marshall said. Until recently, however, the role of sleep apnea as an independent predictor of all-cause mortality has not been well studied, he added.

The Busselton Health Study is an ongoing community-based study in Busselton, Western Australia. For the study, the researchers analyzed data from 400 community-dwelling adults aged 45-60 years. The participants were tested for OSA using a home sleep apnea monitoring device. Sleep apnea was quantified using the respiratory disturbance index (RDI), and moderate to severe apnea was defined as an RDI score of 15 or more respiratory disruptions per hour of sleep.

Complete data were available from 380 participants (278 men and 102 women) after an average of 13.4 years. The mortality rate was significantly higher (33.3%) among the 18 participants with moderate to severe apnea (six deaths), compared with 6.5% among the 77 participants with mild OSA (five deaths) and 7.7% among the 285 participants without OSA (22 deaths).

Compared with people who did not have sleep apnea, the mortality hazard ratio was 6.24 for people with moderate to severe sleep apnea, after the researchers controlled for age, gender, body mass index, mean arterial pressure (as a measure of blood pressure), smoking status, total cholesterol, HDL cholesterol, diabetes status, and physician-diagnosed angina.

"I was suspicious of the size of this effect," Dr. Marshall said. "If you put this same model into an odds ratio, you get an odds ratio of about 10." To put it another way, "sleep apnea has about the same effect on mortality as getting 18 years older," he said.

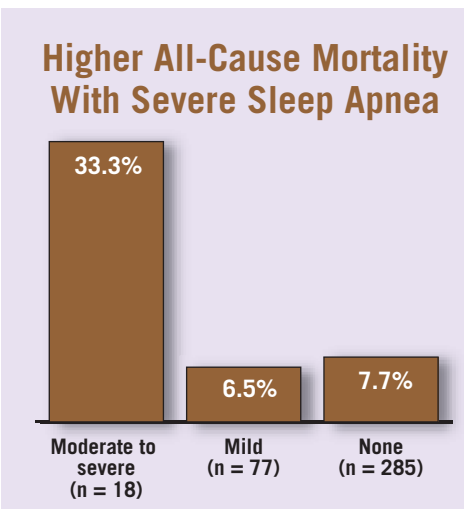
But the results reflect similar recent findings from two studies in the United States—the multicenter Sleep Heart Health Study and the Wisconsin Sleep Study—that also show significant independent associations between OSA and all-cause mortality.

The association between moderate to severe OSA and all-cause mortality in the Busselton Health Study persisted even in a partly adjusted model that did not control for blood pressure. That model was used for comparison because OSA is a known cause of hypertension, Dr. Marshall noted. However, the researchers found no significant association between mild sleep apnea and an increased risk of death, which is good news, he said.

The study was limited by a lack of information about any treatment of sleep apnea in the study group, but the community-based format of the study kept it free of clinical referral bias, said Dr. Marshall.

The findings emphasize the need for randomized controlled trials of sleep apnea treatments that are designed to identify reductions in mortality risk, Dr. Marshall noted.

Dr. Marshall reported that he had no financial conflicts to disclose. ■



Apnea May Promote Insulin Resistance

BALTIMORE — Obstructive sleep apnea in children did not contribute to insulin sensitivity directly, but it was significantly associated with lower adiponectin independent of obesity and puberty in a study of 97 children.

"We hypothesized that obstructive sleep apnea syndrome worsens insulin resistance independently of both obesity and puberty by lowering the adipose-derived insulin sensitizer, adiponectin," noted Dr. Andrea Kelly, an endocrinologist who presented the results of the study at the annual meeting of the Associated Professional Sleep Societies.

Obstructive sleep apnea (OSA) has been linked to metabolic syndrome, but its effect on insulin resistance has not been well studied in children because it is associated with both obesity and puberty, which are recognized contributors to insulin sensitivity, she said.

In this study, Dr. Kelly and her colleagues at the Children's Hospital of Philadelphia collected polysomnography data from 97 children aged 4-18 years (mean age 10.5 years). The researchers categorized the children as pubertal or prepubertal based on Tanner stages and obtained data on fasting blood glucose, insulin, and adiponectin. The children were generally overweight (the average BMI *z* score was 2.1) and the average insulin sensitivity based on homeostatic model assessment was 2.7.

After adjustment for puberty and BMI, none of the polysomnographic indicators of OSA was significantly associated with insulin resistance. But three polysomnographic indicators of OSA—the apnea-hypopnea index, the end-tidal CO_2, and the percentage of time that oxygen saturation was less than 90%—were negatively associated with adiponectin.

More research is needed to confirm a causal relationship between OSA and lower adiponectin, but if such a relationship is confirmed, long-term OSA in children may contribute to an increased risk of insulin resistance, diabetes, and atherogenesis, Dr. Kelly said.

Dr. Kelly reported that she had no financial conflicts to disclose.

—Heidi Splete

DORIBAX™

(doripenem for injection)
for Intravenous Infusion

Brief Summary: The following is a brief summary only. Before prescribing, see complete Prescribing Information in DORIBAX™ (doripenem for injection) labeling.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of DORIBAX™ and other antibacterial drugs, DORIBAX™ should be used only to treat 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 and modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

DORIBAX™ is contraindicated in patients with known serious hypersensitivity to doripenem or to other drugs in the same class or in patients who have demonstrated anaphylactic reactions to beta-lactams.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions: Serious and occasionally fatal hypersensitivity (anaphylactic) and serious skin reactions have been reported in patients receiving beta-lactam antibiotics. These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens. Before therapy with DORIBAX™ is instituted, careful inquiry should be made to determine whether the patient has had a previous hypersensitivity reaction to other carbapenems, cephalosporins, penicillins or other allergens. If this product is to be given to a penicillin- or other beta-lactam-allergic patient, caution should be exercised because cross-hyperreactivity among beta-lactam antibiotics has been clearly documented.

If an allergic reaction to DORIBAX™ occurs, discontinue the drug. Serious acute hypersensitivity (anaphylactic) reactions require emergency treatment with epinephrine and other emergency measures, including oxygen, IV fluids, IV antihistamines, corticosteroids, pressor amines and airway management, as clinically indicated.

Interaction with Sodium Valproate: Carbapenems may reduce serum valproic acid concentrations to subtherapeutic levels, resulting in loss of seizure control. Serum valproic acid concentrations should be monitored frequently after initiating carbapenem therapy. Alternative antibacterial or anticonvulsant therapy should be considered if serum valproic acid concentrations cannot be maintained in the therapeutic range or seizures occur. *[see Drug Interactions]*

***Clostridium difficile*-Associated Diarrhea:** *Clostridium difficile*-associated diarrhea (CDAD) has been reported with nearly all antibacterial agents and may range in severity from mild diarrhea to fatal colitis.

Treatment with antibacterial agents alters the normal flora of the colon and may permit 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 over two 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. *[see Adverse Reactions]*

Development of Drug-Resistant Bacteria: Prescribing DORIBAX™ in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Pneumonitis with Inhalational Use: When DORIBAX™ has been used investigationally via inhalation, pneumonitis has occurred. DORIBAX™ should not be administered by this route.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of labeling:

- Anaphylaxis and serious hypersensitivity reactions *[see Warnings and Precautions]*
- Interaction with sodium valproate *[see Warnings and Precautions* and *Drug Interactions]*
- *Clostridium difficile*-associated diarrhea *[see Warnings and Precautions]*
- Development of drug-resistant bacteria *[see Warnings and Precautions]*
- Pneumonitis with inhalational use *[see Warnings and Precautions]*

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

During clinical investigations, 853 adult patients were treated with DORIBAX™ IV (500 mg administered over 1 hour q8h) in the three comparative phase 3 clinical studies; in some patients, parenteral therapy was followed by a switch to an oral antimicrobial. *[see Clinical Studies (14)* in full Prescribing Information*]* The median age of patients treated with DORIBAX™ was 54 years (range 18-90) in the comparative cUTI study and 46 years (range 18-94) in the pooled comparative cIAI studies. There was a female predominance (62%) in the comparative cUTI study and a male predominance (63%) in the pooled cIAI studies. The patients treated with DORIBAX™ were predominantly Caucasian (77%) in the three pooled phase 3 studies.

The most common adverse reactions (≥ 5%) observed in the DORIBAX™ phase 3 clinical trials were headache, nausea, diarrhea, rash and phlebitis. During clinical trials, adverse drug reactions that led to DORIBAX™ discontinuation were nausea (0.2%), vulvomycotic infection (0.1%) and rash (0.1%).

Adverse reactions due to DORIBAX™ 500 mg q8h that occurred at a rate ≥1 % in either indication are listed in Table 1. Hypersensitivity reactions related to intravenous study drug and *C. difficile* colitis occurred at a rate of less than 1% in the three controlled phase 3 clinical trials.

Table 1: Adverse Reactions† with Incidence Rates (%) of ≥1% and Adverse Events†† Having Clinically Important Differences in Frequency by Indication in the Three Controlled, Comparative DORIBAX™ Phase 3 Clinical Trials

	Complicated Urinary Tract Infections (one trial)		Complicated Intra-Abdominal Infections (two trials)	
System organ class	DORIBAX™ 500 mg q8h (n =376)	Levofloxacin 250 mg IV q24h (n = 372)	DORIBAX™ 500 mg q8h (n = 477)	Meropenem 1 g q8h (n = 469)
Nervous system disorders				
Headache	16	15	4	5
Vascular disorders				
Phlebitis	4	4	8	6
Gastro-intestinal disorders				
Nausea	4	6	12	9
Diarrhea	6	10	11	11
Blood and Lymphatic System Disorders				
Anemia††	2	1	10	5
Renal and Urinary Disorders				
Renal impairment/ Renal failure††	<1	0	1	<1
Skin and subcutaneous disorders				
Pruritus	<1	1	3	2
Rash*	1	1	5	2
Investigations				
Hepatic enzyme elevation**	2	3	1	3
Infection and Infestations				
Oral candidiasis	1	0	1	2
Vulvomycotic infection	2	1	1	<1

* includes reactions reported as allergic and bullous dermatitis, erythema, macular/papular eruptions, urticaria and erythema multiforme

** includes reactions reported as alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, and transaminases increased

† An adverse drug reaction was defined as an undesirable effect, reasonably associated with the use of DORIBAX™ that may occur as part of its pharmacological action or may be unpredictable in its occurrence.

†† An adverse event refers to any untoward medical event associated with the use of the drug in humans, whether or not considered drug-related.

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of doripenem outside of the U.S. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Anaphylaxis
Neutropenia

The following treatment-emergent adverse events (known to occur with beta-lactams including carbapenems) have been reported voluntarily during post-approval use of DORIBAX™ outside of the U.S. They are included due to their seriousness, although it is not possible to estimate their frequency and causality has not been established:

Stevens Johnson Syndrome
Toxic epidermal necrolysis
Interstitial pneumonia
Seizure

DRUG INTERACTIONS

Valproic Acid: A clinically significant reduction in serum valproic acid concentrations has been reported in patients receiving carbapenem antibiotics and may result in loss of seizure control. Although the mechanism of this interaction is not fully understood, data from *in vitro* and animal studies suggest that carbapenem antibiotics may inhibit valproic acid glucuronide hydrolysis. Serum valproic acid concentrations should be monitored frequently after initiating carbapenem therapy. Alternative antibacterial or anticonvulsant therapy should be considered if serum valproic acid concentrations cannot be maintained in the therapeutic range or a seizure occurs. *[see Warnings and Precautions]*

Probenecid: Probenecid interferes with the active tubular secretion of doripenem, resulting in increased plasma concentrations of doripenem. *[see Clinical Pharmacology (12.3)* in full Prescribing Information*]* Coadministration of probenecid with DORIBAX™ is not recommended.

USE IN SPECIFIC POPULATIONS

Pregnancy: Category B: Doripenem was not teratogenic and did not produce effects on ossification, developmental delays or fetal weight following intravenous administration during organogenesis at doses as high as 1 g/kg/day in rats and 50 mg/kg/day in rabbits (based on AUC, at least 2.4 and 0.8 times the exposure to humans dosed at 500 mg q8h, respectively). There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DORIBAX™ is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: Of the total number of subjects in clinical studies of DORIBAX™, 28% were 65 and over, while 12% were 75 and over. Clinical cure rates in complicated intra-abdominal and complicated urinary tract infections were slightly lower in patients ≥ 65 years of age and also in the subgroup of patients ≥ 75 years of age versus patients <65. These results were similar between doripenem and comparator treatment groups.

No overall differences in safety were observed between older and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Elderly subjects had greater doripenem exposure relative to non-elderly subjects; however, this increase in exposure was mainly attributed to age-related changes in renal function. *[see Clinical Pharmacology (12.3)* in full Prescribing Information*]*

This drug is known to be excreted substantially by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function or pre-renal azotemia. Because elderly patients are more likely to have decreased renal function or pre-renal azotemia, care should be taken in dose selection, and it may be useful to monitor renal function.

Patients with Renal Impairment: Dosage adjustment is required in patients with moderately or severely impaired renal function. *[see Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)* in full Prescribing Information*]* In such patients, renal function should be monitored.

PATIENT COUNSELING INFORMATION

- Patients should be advised that allergic reactions, including serious allergic reactions, could occur and that serious reactions require immediate treatment. They should report any previous hypersensitivity reactions to DORIBAX™, other carbapenems, beta-lactams or other allergens.
- Patients should be counseled that anti-bacterial drugs including DORIBAX™ should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When DORIBAX™ 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 DORIBAX™ or other antibacterial drugs in the future.
- Keep out of the reach of children.

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Shionogi & Co. Ltd.
Osaka 541-0045, Japan

Distributed by:
Ortho-McNeil Pharmaceutical, Inc.
Raritan, NJ 08869

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- Clinical efficacy proven in complicated intra-abdominal infections* and complicated urinary tract infections, including pyelonephritis†
- Demonstrated safety and tolerability profiles—no seizures reported in 4 large Phase III clinical trials

Carbapenem potency that breaks through today's gram-negative pathogens‡[1-3]

- Proven in vitro activity vs *P aeruginosa*, Enterobacteriaceae, and *A baumannii*[1-3]

‡ In vitro activity does not necessarily correlate with clinical results.

Please see brief summary of full Prescribing Information on following pages.

DORIBAX™
doripenem for injection

TOUGH TO RESIST

* DORIBAX™ is indicated as a single agent for the treatment of complicated intra-abdominal infections caused by susceptible strains of *E coli, K pneumoniae, P aeruginosa, B caccae, B fragilis, B thetaiotaomicron, B uniformis, B vulgatus, S intermedius, S constellatus,* or *P micros.*

† DORIBAX™ is indicated as a single agent for the treatment of complicated urinary tract infections caused by susceptible strains of *E coli,* including cases with concurrent bacteremia, *K pneumoniae, P mirabilis, P aeruginosa,* or *A baumannii.*

To reduce the development of drug-resistant bacteria and maintain the effectiveness of DORIBAX™ and other antibacterial drugs, DORIBAX™ should be used only to treat 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 and modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Important Safety Information

DORIBAX™ is contraindicated in patients with known serious hypersensitivity to doripenem or other carbapenems, or in patients who have demonstrated anaphylactic reactions to beta lactams.

Serious and occasionally fatal hypersensitivity (anaphylactic) and serious skin reactions have been reported in patients receiving beta-lactam antibiotics. These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens. If an allergic reaction to DORIBAX™ occurs, discontinue the drug. Serious acute anaphylactic reactions require emergency treatment with epinephrine and other emergency measures, including oxygen, IV fluids, IV antihistamines, corticosteroids, pressor amines and airway management, as clinically indicated.

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Clostridium difficile-associated diarrhea (CDAD) has been reported with nearly all antibacterial agents and may range in severity from mild diarrhea to fatal colitis. 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 over 2 months after administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C difficile* may need to be discontinued.

When doripenem has been used investigationally via inhalation, pneumonitis has occurred. DORIBAX™ should not be administered by this route.

Safety and effectiveness in pediatric patients have not been established.

The most common adverse reactions (≥5%) observed in clinical trials were headache, nausea, diarrhea, rash, and phlebitis.

REFERENCES: 1. Evangelista AT, Yee C, Pillar CM, Aranza-Torres MK, Sahm DF, Thornsberry C. Surveillance profiling of doripenem activity against *Pseudomonas aeruginosa* isolated from inpatients and ICU patients: results of the TRUST surveillance initiative. Presented at the 45th Annual Meeting of the Infectious Diseases Society of America (IDSA); 2007: San Diego, CA. **2.** Data on file. Ortho-McNeil-Janssen Pharmaceuticals, Inc. **3.** Jones ME, Draghi DC, Brown NP, Aranza MK, Thornsberry C, Sahm DF, et al. Baseline surveillance profile of Doripenem (DOR) against key gram-negative pathogens encountered in the United States. Presented at the 46th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 2006:San Francisco, CA.

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