The technique causes less pain than conventional approaches while delivering very similar survival rates, Dr. Yoshiya Toyoda said.

**Anteroaxillary Approach Aids Lung Transplant**

**BY MITCHEL L. ZOLER**

*Elsevier Global Medical News*

**BOSTON** — A novel, minimally invasive approach for lung transplant surgery produces small, cosmetically superior incisions and causes less pain than the conventional surgical method, according to results from a series of 116 patients.

In 68 patients treated with an anteroaxillary approach and 48 patients treated with a conventional approach, survival rates to 180 days after surgery were very similar — more than 90% in both groups. Patients in the anteroaxillary group were more likely to be extubated within 48 hours of surgery and less likely to need mechanical ventilation for more than 5 days, Dr. Yoshiya Toyoda reported at the annual meeting of the International Society for Heart and Lung Transplantation.

The anteroaxillary approach also preserved bilateral internal mammary arteries and the sternum, permitted rapid use of cardiopulmonary bypass, resulted in quick chest closure because of a small incision, and required less manipulation of the heart and phrenic nerve.

Because of these and other advantages, the anteroaxillary approach has become the standard surgical method used for lung transplants at the University of Pittsburgh Medical Center, where Dr. Toyoda is a thoracic surgeon and head of cardiopulmonary transplantation.

**Study Links Gene Variation, Biomarker To Asthma Risk**

**BY ELIZABETH MECHCATIE**

*Elsevier Global Medical News*

A protein linked to inflammation and tissue remodeling is a significant biomarker for asthma and poor lung function, and a variation in that protein’s genetic code also is associated with asthma risk and bronchial hyperresponsiveness, according to a study published in the New England Journal of Medicine.

A single-nucleotide polymorphism (SNP) was associated with elevated serum levels of the protein, YKL-40, in several populations, and both the genetic variation and elevated YKL-40 levels were associated with asthma, bronchial hyperresponsiveness, and reduced lung function, according to Carol Ober, Ph.D., of the University of Chicago and her associates in the United States and Germany (N. Engl. J. Med. 2008;358:1682-91).

In an earlier study, some of the same investigators had reported that serum levels of YKL-40 were elevated in patients with asthma. Serum YKL-40 levels also were associated with asthma severity, thickness of the subepithelial basement membrane, and pulmonary function, suggesting that YKL-40 levels could be a biomarker for asthma.

To identify genes that influence serum levels of YKL-40, the investigators conducted a genomewide association study in a group of 632 related Hut terites 6-92 years old (mean age 33) living on communal farms in South Dakota. They also included studies of children with and without asthma.

The investigators hypothesized that “variation in associated genes influences the risk of asthma and bronchial hyperresponsiveness, and is associated with reduced lung function.”

In the current study, they found that among the Hut terites, mean YKL-40 levels were associated with asthma severity, thickness of the subepithelial basement membrane, and pulmonary function.

See Biomarker • page 2

**Guidelines: No to Routine CT Screening**

**BY FRAN LOWRY**

*Elsevier Global Medical News*

**HOLLYWOOD, Fla.** — Routine use of computed tomography screening for non–small cell lung cancer is deemed not ready for prime time in updated guidelines announced at the annual conference of the National Comprehensive Cancer Network.

The guidelines committee on non–small cell lung cancer (NSCLC) chose not to endorse CT screening despite recent data from the International Early Lung Cancer Action Program (IELCAP) showing the technology can detect stage I lung cancer.

“We don’t recommend it routinely. We’ve included [two key] references regarding this, and we all await the national study which should be out in 2009 for the routine use, if needed, for spiral CT,” said Dr. David S. Ettinger, FCCP, Alex Grass Professor of Oncology and professor of medicine, radiation oncology, and molecular radiation sciences at Johns Hopkins University, Baltimore.


The investigators concluded that annual spiral CT screening can detect lung cancer that is curable.

The second study presented a longitudinal analysis of 3,246 asymptomatic current or former smokers who were screened for lung cancer in 1998 and followed for a median of 4 years (JAMA 2007;297:953-61).

See CT Screening • page 4
were 15% higher among those with asthma and 10% higher among those with bronchial hyperresponsiveness, compared with controls. They also found a significant association between an SNP in CHI3L1, a gene encoding for YKL-40, and elevated serum YKL-40 levels, asthma, bronchial hyperresponsiveness, and measures of pulmonary function. In addition, the researchers determined that the same SNP was predictive of asthma from birth through age 5 years in a study of 638 German children, and in a study of 296 adults and children in Chicago. The result “shows that serum YKL-40 level is a highly heritable, quantitative trait in humans and confirms that YKL-40 is a significant biomarker for asthma susceptibility and reduced lung function,” the authors wrote. In addition, genetic variation in CHI3L1 influences serum YKL-40 levels and is associated with the risk of asthma, bronchial hyperresponsiveness, and reduced lung function.” Identifying the rest of the genetic loci that contribute to the differences in serum YKL-40 levels and related proteins “could identify additional genes with a significant effect on the risk of asthma and lung function,” the researchers added.

The findings suggest that the investigators have identified an important genetic risk factor for asthma, but the results need to be confirmed with large studies. Miriam Moffatt, D.Phil., and Dr. William O.C.M. Cookson of the National Heart and Lung Institute at Imperial College, London, said in an accompanying editorial (N. Engl. J. Med. 2008; 358:1725-6).

Genes and Asthma

Biomarker

from page 1

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The findings suggest that the investigators have identified an important genetic risk factor for asthma, but the results need to be confirmed with large studies. Miriam Moffatt, D.Phil., and Dr. William O.C.M. Cookson of the National Heart and Lung Institute at Imperial College, London, said in an accompanying editorial (N. Engl. J. Med. 2008; 358:1725-6).
Son-to-Father Avian Flu Transmission Reported in China

BY JANE SALODOF MCNEIL
Elsevier Global Medical News

ATLANTA — Elderly people have much higher rates of venous thromboembolism than younger people do. They also tend to have elevated levels of D-dimer—which can make D-dimer testing less useful in predicting the risk of recurring blood clots when patients are aged 65 and older.

The relationship between exponentially increasing venous thromboembolism (VTE) rates in the elderly and rising D-dimer levels presents a public health and scientific problem of unrecognized dimensions.

"Older age reduces the clinical usefulness of D-dimer testing. ... We probably need age-adjusted cutoffs in older people," Dr. Kenneth A. Bauer, a professor of medicine at Harvard Medical School, Boston, said during the special session at the annual meeting of the American Society of Hematology.

"We really do need more work done in D-dimer, though it is the most promising of the markers that we see in predicting recurrence risk," said Dr. Bauer, who is also chief of the hematology section at the Veterans Affairs Boston Healthcare System and director of thrombosis research at Beth Israel Deaconess Medical Center, Boston.

Incidence of venous thromboembolism rises exponentially starting at age 45 years. Dr. Cushman

Incidence of venous thromboembolism rises exponentially starting at age 45 years, reported Dr. Mary Cushman of the University of Vermont, Burlington. VTE is three times more common in people aged 65 years and older, compared with those aged 45-64 years. While VTE patients are stratified by age, 70% are 60 years and older.

Just why VTE incidence increases with age is not clear, but Dr. Cushman offered several hypotheses: increased comorbidities and frailties, impaired mobility, inflammation, alteration of vein health, sarcopenia, and increased coagulation potential.

Despite limited data, she said, the evidence to date makes clear that the impact is also worse in the elderly, with rates of death, recurrence, post-thrombotic syndrome, and treatment complications rising with each decade of life. The elderly "are more likely to fail treatment than those under age 65," she said.

In healthy elderly individuals, however, researchers have found high levels of many coagulation activation markers, including D-dimer, a fibrin degradation product released when blood clots.

"D-dimer really is a composite of thrombin activation and then plasma dissolution of the fibrin that is normally formed. There are low levels of D-dimer that we measured in normal healthy people," Dr. Bauer said.

The fact that D-dimer is heterogeneous has led to issues in using and standardizing D-dimer assays, he noted, contrasting it with other coagulation markers that are discrete polypeptides with defined molecular weights.

"D-dimer is a physiological variable and can vary over time," Dr. Bauer said, discussing a study of centenarians conducted in Italy (Blood 1995;85:3144-9).

Investigators compared 25 healthy centenarians with two control groups of healthy people aged 18-50 years and 51-69 years. Each of these groups also was made up of 25 people.

The healthy centenarians showed laboratory signs of coagulation activation, including high levels of proteins that can predict cardiovascular disease in middle-aged people. When the D-dimer concentrations were highly elevated in the centenarians: 323 ng/mL, compared with 29 ng/mL in the younger control group and 50 ng/mL in the middle group. That healthy centenarians have significantly higher levels of D-dimer suggests that increased D-dimer "is not necessarily a bad thing. It is consistent with long life," Dr. Bauer commented.

While many coagulation activation markers increase with age, he focused on D-dimer because it has the potential to stratify recurrence risk in patients after treatment for their first idiopathic VTE and thereby identify who would benefit from extended anticoagulation.

Among several studies showing higher recurrence risk in patients with elevated D-dimer levels, he highlighted a multicenter investigation conducted in Italy (N. Engl. J. Med. 2006;355:1780-9).

In that study, D-dimer levels were tested 1 month after anticoagulation was stopped in patients who had a first unprovoked deep vein thrombosis or pulmonary embolism. Patients with normal levels did not resume therapy.

Those with "abnormal" D-dimer levels were randomly assigned to resuming or staying off treatment. Of the patients with elevated D-dimer levels, 74% were aged 65 years and older.

At a median follow-up of 1.4 years, 10.7% of untreated patients with abnormal D-dimer levels had a recurrence, compared with 4.4% of those with normal levels (hazard ratio 2.27).

When untreated patients were stratified by age, Dr. Bauer said the risk of recurrence was less in the elderly; they had a hazard ratio of 1.63, compared with 4.40 for those younger than age 65.

Among patients with normal D-dimer levels, however, he said recurrence was higher in the elderly.

In an interview immediately after the session, he cautioned against taking an alarmist stance when elderly patients present with high D-dimer levels.

"We are getting a lot of elderly referred because they have chronically elevated D-dimer tests with no history of thrombosis," he said. "One needs to be aware that [this is] probably something that goes along with age."
**FDA Panel Offers Specifics for Revised CAP Trials**

By Jamie Hamm

“The Pink Sheet Daily”

Design of trials for community-acquired pneumonia drugs would face greater specificity but no major changes, according to recommendations from the Federal Drug Administration’s Anti-Infective Drugs Advisory Committee.

The panel said at its April 2 meeting that a noninferiority margin of 10% in active-control noninferiority trials should be acceptable to prove efficacy of community-acquired pneumonia (CAP) drugs. The FDA is working to update its guidance on CAP trial design and sought committee insight on how to translate the limited data from historic antibiotic trials into a scientifically verifiable treatment effect to serve as the basis for comparison to new antibiotics.

The committee discussed whether mortality data from CAP trials of penicillin, sulfonamides and tetracyclines in the early 1900s can serve to establish a treatment effect for comparator drugs on clinical outcomes and in different levels of disease severity.

Despite complications with data interpretation, the panel settled on the 10% noninferiority margin after unanimously agreeing that a treatment effect can be quantified for CAP studies of IV drugs in hospitalized patients, and they voted 10-3 that the same could be said for oral formulations in outpatient CAP patients.

The discussion of CAP clinical trial design is part of the FDA’s efforts to provide clearer guidance on antibiotic trial requirements.

Noninferiority trials are a popular option for anti-infectives, but the FDA has issued guidance requiring that superiority trials be conducted for several self-resolving, community respiratory tract infections.

The FDA expressed concerns about use of noninferiority trials in CAP as well as at a recent meeting that industry has provided the agency little data in support of the design. However, there is general consensus that conducting superiority or placebo-controlled trials in CAP patients is unrealistic. All clinical trials recently submitted to the FDA for a CAP indication have been noninferiority trials.

However, proper noninferiority trial design in CAP is challenging. The treatment effect for active comparators is unknown because no placebo-controlled trials have been conducted for CAP since the 1940s; and the conduct of further placebo-controlled trials is widely considered unethical due to the known value of antibiotics. The panel voted unanimously against placebo-controlled trials even for mild to moderate CAP.

Moreover, active comparator superiority studies are unattractive to industry due to the likelihood of failure to demonstrate superiority in the self-resolving condition, even for effective drugs.

Thus, development of new agents to treat CAP fails to active comparator noninferiority studies for which FDA is determined by the mortality in the historical data.

All of the committee members except one thought that it is fine to rely on the prior clinical data to evaluate mortality for CAP candidate strategies.

“We have far more patients with underlying conditions and comorbidities—it’s very different right now from what it was in the 1980s. It’s so different to interpret the data, I’m not sure we’re doing anybody a favor by dealing with it,” said one temporary voting member, Dr. Daniel Musher of Baylor College of Medicine.

The rest of the panel debated the appropriateness of evaluating measures of clinical efficacy for the new products.

Temporary voting member Dr. Thomas Fleming, University of Washington, argued that the extrapolation could not be statistically justified. “I think the fundamental principle that first needs to be recognized is that margin in how we use are specific to end point … Justifying the margin using data for one end point to another is conceivably possible but enormously complicated.”

He urged that “mortality is still a highly clinically relevant end point, as well as one that historical data provide us the best sense as to what the effect of the active comparator is, given that’s the base to do a valid noninferiority assessment.”

“Sixty years ago, they didn’t have any rescue medications,” Jürgen Venitz, Medivation, Virginia, said. “I think there are other things that allow you to make that translation. I believe that we can translate quantitatively the mortality difference that they found 50-plus years ago to clinical success as we do it today.”

The FDA seemed open to translating mortality data to support trials evaluating clinical outcomes. “It seems very reasonable to take what constitutes failure in the modern world and equate that with mortality,” Office of Drug Evaluation Director Robert Temple said.

The panel agreed that a treatment effect can be quantified for noninferiority studies of oral formulations for outpatient CAP. There was general consensus that the same end points used for severe CAP could be used in testing for outpatient CAP drugs.

Those in favor of extrapolating the mortality data to the outpatient setting noted that modern medicine allows many patients that would have been hospitalized and placed on intravenous therapy at the time of the historical studies to be today treated as outpatients placed on oral antibiotics.

“I think everything we heard made us think that you continue to use that kind of endpoint here just as you would in the more severe illness,” Mr. Temple said.

“What I heard is that people think that the data we have on severe illness is probably now applicable to people who aren’t necessarily hospitalized because the modern world makes that unnecessary. But that really means they’re fairly sick or have severe disease—we’re not talking about things that you ordinarily think of as just really mild.”

The panel also voted unanimously that establishing efficacy in severe CAP supports the drug’s effect in less severe CAP, even though the effect of the drug has not been directly studied for that indication.

The panel also weighed in on how to determine disease severity. “The idea is to enrich for bacterial pneumonia,” temporary voting member Scott Dowell, Centers for Disease Control and Prevention, said.

“The way you define CAP may be one of the most important things we do to enrich for those patients who actually have bacterial pneumonia,” he noted.

“What seems reasonable and possible to do is you start out with a … clinical syndrome that says ‘I think there’s a typical bacterial pneumonia,’” said AstraZeneca Infection Clinical VP John Rex, the non-voting industry representative.

“The classic syndrome needs to be an abrupt onset of a febrile syndrome that points to the chest, with a change on the chest x-ray, and probably with the ability to produce some sputum. Those things together suggest a bacterial etiology and it’s the acuity of the presentation,” he said.

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Dr. Mark Metesky, FCPP comments: Sanity prevails at the FDA. While the desire for trials that prove that new antibiotics for CAP are better than currently available ones is understandable, the potential for lack of superiority and the prohibitive cost of such trials would likely dry up the pipeline of new antibiotics for CAP.

Dr. Ettinger disclosed the following affiliations and significant relationships: AstraZeneca Pharmaceuticals LP; Bristol-Myers Squibb Co.; Eli Lilly & Co.; GlaxoSmithKline; Merck & Co.; MGI Pharma Inc.; Pfizer Inc.; and Sanofi-Aventis U.S.

Dr. Michael Alberts, FCPP comments: All hope that lung cancer screening by low-dose CT will be shown to provide a mortality benefit. Studies are underway that are designed to address this hypothesis.

Until such information is available and because of the very real risks inherent in screening (e.g., false positive results, unnecessary procedures, radiation exposure, psychological stress), the ACCP does not recommend screening outside the protections afforded by a clinical trial.

**Adjuvant Tx Reviewed**

CT Screening • from page 1

The investigators concluded that screening for lung cancer can increase the rate of diagnosis and treatment, but might not meaningfully reduce the risk of advanced disease or death.

In place of routine screening, the guidelines committee recommended that high-risk individuals participate in a category 2B designation CT screening protocol.

If such a trial is not available, or if an individual is not eligible to participate in a trial, then he or she should go to a center of excellence with expertise in radiology, pathology, cytology, thoracic surgery, and general supportive care to identify and evaluate experimental options in lung cancer treatment to discuss the potential risks and benefits before having a screening CT.

If the individual opts for screening, the committee recommended that the I-ELCAP screening protocol be followed.

In other updates, the committee decided to add a category 3 recommendation for use of adjuvant treatment of stage I NSCLC. “This indicates major disagreement among members as to which patients should get adjuvant therapy,” commented Dr. Ettinger.

For stage IIA disease with negative margins, the committee replaced a previous recommendation for chemoradiation by chemotherapy with a new recommendation for mediastinal radiation therapy.

In addition, surveillance recommendations for all NSCLC stages now include a chest CT every 4-6 months for 2 years in lieu of every 6 months. Again, this was a category 2B designation among panel members, Dr. Ettinger said.

The committee also designated cisplatin/etoposide and cisplatin/vinblastine chemotherapeutic regimens as preferred therapies. Paclitaxel/carboplatin was given a category 2B designation.
Diabetics Show Faster Decline in Forced Vital Capacity

Lung function declines more rapidly in diabetic individuals than in those without the disease, according to the results of a longitudinal, prospective analysis of more than 11,000 adults.

Over a 3-year period, individuals with diabetes had a decline in forced vital capacity (FVC) of 64 mL/year, compared with a decline of 58 mL/year in people without diabetes, a small but significant difference.

The decline in lung function has implications for clinical outcomes in elderly diabetics who develop respiratory or cardiovascular complications, wrote Hsin-Chieh Yeh, Ph.D., of the departments of epidemiology and medicine at Johns Hopkins University, Baltimore, and his colleagues (Diabetes Care 2008;31:741-6).

The researchers analyzed longitudinal data from the Atherosclerosis Risk in Communities (ARIC) Study—a community-based prospective cohort of 15,792 adults aged 45-64. The participants were recruited from North Carolina, Mississippi, Minnesota, and Maryland. The analysis included data from baseline to 3 years of follow-up. Those of ethnicity other than black or white were excluded.

The researchers also excluded those in the upper or lower 1% of FVC, forced expiratory volume in 1 second (FEV1), or FEV1/FVC ratio at baseline or at 3-year follow-up, as these individuals were assumed to be outliers.

The final study sample included 11,262 subjects—1,100 with diabetes at baseline and 10,162 who were nondiabetic at baseline. At baseline and at the 3-year follow-up, FVC and FEV1 were measured according to recommendations from the Epidemiology Standardization Project and the American Thoracic Society. Subjects were classified as having diabetes if they had a fasting glucose level of 126 mg/dL, a nonfasting glucose level of at least 200 mg/dL, were currently using a diabetes medication, or answered positively to the question “Has a doctor ever told you that you had diabetes (sugar in the blood)?” Glycosylated hemoglobin A1c levels were available for all 1,637 cases of prevalent type 2 diabetes at the second ARIC visit, as well as for a subgroup of 598 randomly selected nondiabetic individuals (from a previous study).

Compared with nondiabetic subjects, diabetics were more likely to be male, older, African American, and less physically active, and to have a greater body mass index and a higher waist-to-hip ratio. Diabetic subjects also had a greater prevalence of hypertension and higher white blood cell counts and fibrinogen levels.

Diabetics had significantly lower FVC, FEV1, FVC% predicted, and FEV1% predicted—by 133 mL, 72 mL, 3.6%, and 2.4%, respectively—than did nondiabetic subjects in cross-sectional analyses, after adjustment for age, gender, race, BMI, waist circumference, height, pack-years of smoking, sport activity index, educational level, and ARIC field center. These relationships were graded by fasting glucose, HbA1c level, diabetes duration, and intensity of diabetes treatment, and were independent of traditional risk factors for lung function decline, such as age, smoking status, and central obesity.

Additional analysis showed that inflammatory markers—white blood cell count and plasma fibrinogen—attenuated the observed relationships only slightly.

In an accompanying editorial, Dr. Connie C.W. Hsia, FCCP, and Dr. Philip Raskin said that the study further advances the idea of the lung as a target of diabetic injury. “Think of the lung as a crime scene, with inflammation, which is common in diabetics, the link for this observation. Cumulative loss of pulmonary reserves eventually aggravates tissue hypoxia associated with any form of angiopathy in distal organs that ultimately underlies diabetic morbidity and mortality,” wrote Dr. Hsia and Dr. Raskin, both of the internal medicine department at the University of Texas Southwestern Medical Center, Dallas (Diabetes Care 2008;31:828-9).

Dr. Nicola Hanania, FCCP, comments: This study analyzed data from on a large prospective cohort study and compared lung function changes in diabetics and nondiabetics over 3 years. The authors conclude that diabetics have a faster decline in lung function parameters, especially FVC, compared with subjects without diabetes. This is an interesting observation that may explain the systemic comorbidities often seen in diabetics. Of note, the two cohorts compared were not age-, gender-, or race-matched, although correction for these confounding factors—as well as for differences in smoking status and body mass index—was done based on the authors’ statements. Future studies will need to investigate the mechanism(s) of this difference in lung function decline. Systemic inflammation, which is common in diabetics with metabolic syndrome, may be the missing link for this observation.
Follow-Up Care Lacking for Lung Cancer Survivors

Survivors are at high risk for other primary cancers, cardiovascular disease, and osteoporosis.

BY FRAN LOWRY
Elsevier Global Medical News

Hollywood, Fla. — Cure rates for locally advanced lung cancer are increasing, but our understanding of long-term follow-up care remains a challenge for the growing number of lung cancer survivors, Dr. Mark G. Kris, FCPC, told attendees at the annual conference of the National Comprehensive Cancer Network.

"Tens of thousands of people a year are leaving their surgeon’s office and are told 'goodbye and good luck,' despite the fact that they’ve had a lung removed," said Dr. Kris, chief of the thoracic oncology service at Mount Sinai Sloan Kettering Cancer Center in New York.

"If you’ve had a bypass surgery, you can get Medicare to pay for your cardiac rehabilitation, but if somebody removes your lung, there is nothing," he said. "You go to your surgeon’s office to your apartment or your home, and that’s it. Hasta la vista, baby. It’s time that changed."

Dr. Kris made follow-up care an issue during a presentation of updated National Comprehensive Cancer Network (NCCN) recommendations for the management of local and locally advanced non–small cell lung cancer (NSCLC). He attributed improved survival to advances in chemoradiation therapy and surgery.

"We have the ability to cure patients with advanced non–small cell lung cancer. There are tens of thousands of patients being cured of lung cancer every year, but (follow-up care) is something that is too often neglected. We need to keep this in mind," he said, listing areas that require long-term attention.

Because of their exposure to tobacco, NSCLC survivors are at very high risk—from 1% to 5% per year—for developing another primary cancer. As a result, Dr. Kris said, they need careful surveillance and should be asked about their smoking status. Indeed, he said he believes smoking status should be documented in the medical record at each follow-up office visit.

Survivors of lung cancer are also at risk for other smoking-related illnesses, such as chronic obstructive pulmonary disease and heart disease, he continued, and should be followed accordingly. In addition, radiation to the chest accelerates cardiovascular disease. As a result, lung cancer survivors need careful cardiac monitoring, including stress testing and lipid monitoring.

Radiation also accelerates osteoporosis, for which Dr. Kris said lung cancer survivors need to be prospectively treated, regardless of their general bone density, to protect against bone loss.

"These people have a lot of unmet needs. The time has come to pay attention to these needs," he said.

In his rundown of updates to the NCCN guidelines for local and locally advanced NSCLC, Dr. Kris noted the following on behalf of the guidelines committee:

- The standard of care remains anecdotal resection, although ways of choosing lesser surgeries are currently an area of investigation. "To the surgeons in the audience, I know it doesn’t make a lot of sense, when you have that one right lower lobe, but that is still what we recommend."

- Whereas guidelines for other cancers recommend a number of nodules to be sampled, in lung cancer, the recommendation covers the number of stations to be sampled.

- "That number is three," Dr. Kris said.

- For stage IA NSCLC, the recommended treatment remains surgery. Adjuvant therapy is not recommended, but this negative recommendation was not unanimous. "It was a category 3 designation, so there was absolutely no agreement among the panel."

- The guidelines committee was in complete agreement on use of adjuvant cisplatin-based chemotherapy for completely resected patients with stages II and IIIA disease.

- It also gave a category 1 recommendation—its highest level of endorsement—for mediastinal radiation for IIIB disease.

- "The combination of cisplatin and vinorelbine is the most studied combination for adjuvant therapy for resected NSCLC and is the standard of care."

- The data are clear that adjuvant radiation has no benefit for clinically resected patients with stage I or stage II disease. Consensus among panel members was not as strong, however, regarding stage IIIA disease because of a lack of prospective level 1 evidence.

Dr. Kris disclosed that he is a consultant for Bayer HealthCare, Boehringer Ingelheim GmbH, Bristol-Myers Squibb Co., Eli Lilly & Co. GlaxoSmithKline, Novartis Pharmaceuticals Corp., and Pfizer Inc. He receives grant and research support from sanofi aventis U.S.

Salad Consumption May Influence Lung Cancer Risk

E ating at least four servings of salad vegetables per week is associated with a reduction in the risk of developing lung cancer in non-Hispanic whites, reported researchers at the University of Texas M.D. Anderson Cancer Center, Houston.

Compared with those who consumed four or more servings of salad per week, "those who consumed three or less than three servings per week actually have a two- to threefold increased risk of lung cancer among current smokers, former smokers, and never smokers," study investigator Michele Forman, Ph.D., a professor of epidemiology at the university, said at a press briefing. The briefing was held in conjunction with an annual conference on cancer prevention sponsored by the American Association for Cancer Research.

In a study that included more than 3,800 patients and controls, the researchers used models for current smokers, former smokers, and never smokers that were developed from an ongoing case-control study.

In particular, the researchers wanted to look at possible effects of fruit and vegetable consumption because “there has been a number of components in fruits and vegetables that has been associated with reduction in the risk of lung cancer in different populations,” Dr. Forman said in an interview.

First, they added fruit consumption to the lung cancer risk prediction models for all three groups (current, former, and never smokers). Fruit intake had no effect on lung cancer risk for any of the groups.

Next, they looked at vegetables. Salad vegetables included carrots, lettuce, onions, and others, the consumption of which individually is a predictor of lung cancer risk. The researchers also adjusted for factors that could affect diet, such as socioeconomic factors and age.

They found that among current smokers, those who consumed three servings of salad per week had a more than twofold increased risk (odds ratio 2.09) of developing lung cancer, compared with those who consumed four or more servings per week. In the same group, those who consumed fewer than three servings per week had a slightly higher risk of developing lung cancer (OR 2.15). The results were similar for former smokers.

Among current smokers, those who ate three or fewer servings of salad per week had an almost threefold increased risk of lung cancer (OR 2.73), compared with smokers who ate four or more salad servings per week.

There was little physical activity meaning among those with lung cancer, Dr. Forman said. However, gardening was reported in both healthy controls and those with lung cancer.

The researchers found that among current, former, and never smokers, gardening at least once a week was associated with a 30%-40% reduction in lung cancer risk.

Among never smokers, those who worked in the garden once or twice a week had a 40%-46% lower risk of lung cancer, compared with those who did not report any gardening. Results were similar for former smokers.

Among current smokers, gardening once or twice per week was associated with a 33%-45% reduction in risk.

Now, gardening is a fun physical activity. It could be anything from cutting flowers to planting a tree," Dr. Forman said. The activity questionnaires did not provide enough detail to determine what respondents meant by “gardening." Despite this range of exertion, one common element to all gardening activities is sun exposure, and therefore, vitamin D exposure.

“These are very preliminary findings,” Dr. Forman said. The researchers are planning to look more closely at the data to determine if their study population was a selective subset of individuals with a healthier lifestyle in general.
Hospitals Tackle New Joint Commission Safety Goal

**BY MARY ELLEN SCHNEIDER**
Elsevier Global Medical News

The Joint Commission’s new 2008 patient safety goal of requiring a process to respond quickly to a deteriorating patient is being mistakenly interpreted at some hospitals as a mandate for “rapid response teams” or “medical emergency teams.”

Further, at some organizations that already have rapid response teams, staff have expressed concerns they will need to redo their established systems.

Dr. Peter Angood, vice president and chief patient safety officer for the Joint Commission, said such presumptions are incorrect.

“Hospitals are simply being asked to select a ‘suitable method’ that allows staff members to quickly request assistance, when to make that call, and to document the success or failure of the system that is in place. ‘This is not a goal that states there needs to be a rapid response team,’ Dr. Angood said.

Many institutions in the United States have implemented rapid response teams, and the data on their efficiency are generally good, but not every study has been positive, Dr. Angood said. As a result, officials at some hospitals are looking forward to move forward with a more basic approach to developing the response plan, said Dr. Robert Wachter, chief of the division of hospital medicine at the University of California, San Francisco. And perhaps the biggest role for the hospitalist is in providing the around-the-clock coverage that could negate the need to call the formal response team as often, he said.

While the Joint Commission’s requirement might seem like a greater challenge to small hospitals, Brock Slabach, senior vice president for member services at the National Rural Health Association, dictated as part of the Institute for Health Improvement’s 5 Million Lives Campaign, a national patient safety campaign designed to reduce harm in U.S. hospitals.

Of the 3,800 hospitals enrolled in the 5 Million Lives Campaign as of January, about 2,700 have committed to using rapid response teams, according to IHI. This idea is catching on, said Kathy Duncan, R.N., faculty for the 5 Million Lives Campaign.

The cost of implementing these types of teams varies, she said. About 75% of hospitals in the campaign have done this with zero increase in full-time employees, she said. For most staff involved, this is just an additional task. Investment is required for training team members, which can be costly at the outset, she said. Hospitals also need to invest time to educate the rest of the staff on when and how to call for assistance.

Ms. Duncan’s advice for implementing whatever process hospitals choose to respond to the Joint Commission’s goal is to start by assessing what resources are available. Next, don’t just jump into implementation, but take the time to test the process and figure out how people will request assistance, when to make that call, and who should respond. “Start small with a pilot process,” Ms. Duncan said.

**Implementing a Response Plan**

Because of the complexity of implementing a process to respond quickly to a deteriorating patient, officials at the Joint Commission are giving hospitals time to develop and phase in their program.

By April 1, the first deadline, hospital leaders were required to assign responsibility for the oversight, coordination, and development of the goals and requirements. By July 1, there needs to be an implementation work plan in place that identifies the resources needed. By Oct. 1, pilot testing in one clinical area should be underway.

The Joint Commission is serious about enforcing these implementation milestones, Dr. Angood said. Hospitals that don’t meet the quarterly deadlines will be docked points on their evaluation.

For 2009, hospitals will need to comply with the following six “implementation expectations” set out by the Joint Commission:

1. Select an early recognition and response method suitable to the hospital’s needs and resources.
2. Develop criteria for how and when to request additional assistance to respond to a change in a patient’s condition.
3. Empower staff, patients, and/or families to request additional assistance if they have a concern.
4. Provide formal education about response policies and practices for both those who might respond and those who might request assistance.
5. Measure the utility and effectiveness of the interventions.
6. Measure cardiopulmonary arrest rates, respiratory arrest rates, and mortality rates before and after implementation of the program.

**Shock Index and Age Improved Prediction of Mortality**

**BY ROBERT FINN**
Elsevier Global Medical News

**Huntington Beach, Calif.**—In patients older than 55 years, multiplying a patient’s age by the Shock Index—a ratio of heart rate to systolic blood pressure—provides a better predictive rule than the Shock Index alone, Dr. Ben L. Zarzaur said at the Aca
demic Surgical Congress.

The Shock Index (SI) has long been known to provide a better predictive rule of thumb than heart rate or blood pressure alone, Dr. Zarzaur said. Better still are several measures such as the Injury Severity Score, the Revised Trauma Score, and the Trauma Injury Severity Score—but they use relatively complex equations and can be difficult to calculate in the resuscitation room.

In contrast, the Shock Index is simple to calculate but does not take into account the effect of patient age.

Dr. Zarzaur of the Presley Memorial Trauma Center at the University of Tennessee, Memphis, and colleagues conducted a retrospective cohort study that involved a total of 16,077 patients, aged 18-81 years, who were admitted to the trauma center between 1996 and 2005. All were victims of blunt trauma, and all arrived with a palpable pulse of at least 10 beats per minute and a systolic blood pressure of at least 30 mm Hg. The investigators excluded patients with a primary outcome of blood transfusion during that time period as a secondary outcome. They performed an analysis of the area under the receiver operating curves (ROC), a statistical method that quantifies the balance of sensitivity and specificity, to determine which measures were the best.

Among the younger patients, SI alone had a significantly larger ROC area than did pulse rate, systolic blood pressure, or age alone, Dr. Zarzaur said. An SI score greater than 0.8 successfully predicted significant early mortality and transfusion in this age group.

In the older patients, on the other hand, age multiplied by SI had a larger ROC area than did the other measures. When age was multiplied by SI, a resulting product that was 50 or greater successfully predicted significant early mortality and transfusion in this age group.

Dr. Zarzaur declared that he had no financial conflicts related to the study.

I
Universal MRSA Screening Slashed Rates by Half

Treatment of patients who tested positive decreased prevalence of four types of MRSA.

By Heidi Splete

A scoring method that combines bilirubin and lactate values with the specific etiology of acute liver failure better predicts death or the need for transplant than do existing methods, Dr. Johannes Hadem and colleagues reported in an article appearing in the March 2008 issue of Clinical Gastroenterology and Hepatology.

The new scoring method, known as the bilirubin-lactate-etiology (BiLE) measure, has a sensitivity of 79% and a specificity of 84% for predicting death or the need for transplant if the patient’s score is greater than 6.9.

These sensitivity and specificity values are significantly better than are other measures including the Model for End-Stage Liver Disease (MELD) and the Simplified Acute Physiology Score III (SAPS-III), according to Dr. Hadem of Hannover (Germany) Medical School, and his colleagues.

The BiLE score is simple to calculate and is especially suited to bedside use immediately after admission to the intensive care unit, wrote the investigators.

But because of the diversity of acute liver failure etiologies in different regions of the world, the BiLE score will need to be validated in other centers and with other patient cohorts.

In order to develop the BiLE score, the investigators conducted a retrospective analysis of 402 patients from the intensive care unit of a single institution who fulfilled the diagnostic criteria for acute liver failure.

BiLE Tops Other Liver Transplant Scoring Methods

By Robert Finn

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In order to develop the BiLE score, the investigators conducted a retrospective analysis of 402 patients from the intensive care unit of a single institution who fulfilled the diagnostic criteria for acute liver failure.

Of those patients, a total of 39 survived for a period of at least 8 weeks without the need for orthotopic liver transplant (OLT), 18 died without OLT, 5 died following OLT, and 40 survived following OLT. In all, 79 of the patients (77%) survived to week 8.

THE BiLE SCORE ACHIEVED A SENSITIVITY OF 79% AND A SPECIFICITY OF 84% FOR PREDICTING DEATH OR THE NEED FOR TRANSPLANT.

For the purposes of the study, patients who had hepatic dysfunction were diagnosed with acute liver failure if they had hepatic encephalopathy, acute-onset increase of the international normalized ratio (INR) greater than 1.5, and the absence of signs of chronic liver disease during the clinical and the ultrasound examinations.

The investigators did not find any predominant etiology for acute liver failure among the patients in the study. Cryptogenic acute liver failure was the etiology in 21 patients, acute hepatitis B in 18, acute ethanol ingestion in 16, Budd-Chiari syndrome in 9, phenprocoumon toxicity in 7, idiosyncratic drug reactions in 5, Amanita phalloides ingestion in 5, Wilson’s disease in 5, and idiopathic hyperbilirubinemia in 3. The remaining 5 patients had etiologies classified as “other.”

In comparing patients who survived with those who died or required a liver transplant, the investigators found that 15 different laboratory values and other characteristics showed statistically significant differences.

Multivariate linear regression revealed that bilirubin and lactate levels were the most predictive of survival. Patients who survived without undergoing transplantation had a mean bilirubin level of 1.6 micromol/L, compared with 263 micromol/L in the liver transplantation or death group.

Similarly, patients who survived without transplantation had a mean lactate level of 2.9 mmol/L, compared with a mean value of 4.7 mmol/L in the liver transplantation or death group.

There were significant differences between the groups in etiology as well. Patients with cryptogenic acute liver failure, Budd-Chiari syndrome, or phenprocoumon toxicity were more likely to die or require transplantation, while those with acetaminophen toxicity were more likely to survive without the need for transplantation.

The investigators designed the BiLE score empirically. In order to bring bilirubin and lactate into the same range of values, the equation calls for dividing bilirubin concentrations in micromol/L by 100. To this figure, one adds the lactate concentration in mmol/L and then adds or subtracts a value depending on the etiology (see sidebar).

Using a cutoff value of 6.9 to predict death or the need for transplantation, the investigators found that the BiLE score achieved a sensitivity of 79%, a specificity of 84%, a positive predictive value of 89%, and a negative predictive value of 71%.

The sensitivity of the BiLE score was 100% in patients with cryptogenic acute liver failure.

In contrast, using the value of lactate alone with a cutoff of 3.5 mmol/L, achieved a sensitivity and specificity of 59% and 66%, respectively.

The MELD score with a cutoff of 12 achieved a sensitivity and specificity of 65% and 69%, respectively, while the King’s College Criteria achieved a sensitivity and specificity of 58% and 82%, respectively.

The investigators stated that they had no conflicts of interest to report.

Calculating the BiLE Score

The calculation method for the BiLE score is as follows:

Bilirubin (micromol/L)/100 + lactate (mmol/L) + 4 (in the case of cryptogenic acute liver failure, Budd-Chiari syndrome, or phenprocoumon toxicity) + 2 (in the case of acetaminophen toxicity) + 0 (in the case of other etiologies)

BiLE scores above 6.9 are predictive of death or liver transplantation.

The BiLE score achieved a sensitivity of 79%, a specificity of 84%, a positive predictive value of 89%, and a negative predictive value of 71%.

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The investigators stated that they had no conflicts of interest to report.
CINCINNATI — Control of blood glucose levels through intensive insulin therapy has been shown to reduce morbidity both in surgical and medical ICU patients, as well as mortality in surgical ICU patients. Results of a retrospective study now suggest that implementation of this therapy in burn patients may reduce the rate of infectious complications but not mortality.

Maintaining mean blood glucose levels of less than 140 mg/dL reduced the rate of pneumonia, ventilator-associated pneumo-

nia, and urinary tract infections in 71 burn patients who received intensive insulin therapy, compared with 81 burn patients in the same ICU during the year before the protocol was implemented. Dr. Mark R. Hemmila reported at the annual meeting of the Central Surgical Association.

But some discussants at the meeting questioned whether certain weaknesses in the study’s design and differences in patient characteristics accounted for some of the observed results.

During the first year of an intensive insulin therapy protocol (July 2005 to June 2006), Dr. Hemmila and his colleagues at the University of Michigan, Ann Arbor, sought to bring burn patients’ blood glucose levels to less than 140 mg/dL. In the previous year (July 2004 to June 2005), burn pa-

tients had received an insulin drip protocol when their blood glucose levels exceeded 130 mg/dL.

The patients in each group had a mean age in the early 40s, and close to three-

fourths in each group were men. The investigators excluded patients with con-

comitant trauma and burn injuries or desquamating skin diseases.

The control and intensive insulin therapy groups had similar blood glucose levels upon admission (142 mg/dL vs. 130 mg/dL, respectively) and in terms of daily average (135 mg/dL vs. 129 mg/dL, as well as over-

all mean during their hospital stay (127 mg/dL vs. 126 mg/dL)). The intensive in-

sulin therapy and control groups each spent a similar percentage of time in the hospital with a mean daily blood glucose level greater than 140 mg/dL (22% vs. 35%, respectively). But compared with patients in the control group, those who were treated with intensive insulin therapy spent a sig-

ificantly lower percentage of their time in the hospital with a maximum mean daily blood glucose level greater than 200 mg/dL (11% vs. 17%).

In multivariate analyses that adjusted for age, gender, the percentage of total body surface area burned, and inhalation injury, adding intensive insulin therapy did not significantly improve the outcomes ob-

tained in burn patients in the year before the therapy was implemented. There were no improvements in mortality (7% vs. 9%, respectively) or in intensive insulin vs. control patients), mean length of stay in the ICU (3 vs. 9 days), mean length of stay in the hospital overall (10 vs. 17 days), and mean number of days requiring ventilation (3 vs. 6 days).

However, intensive insulin therapy sig-

ificantly reduced rates of pneumonia overall (16% vs. 37%), ventilator-associated pneumo-

nia (10% vs. 31%), and urinary tract infection (6% vs. 22%).

The odds of developing infection were more than 11 times higher in patients with a maximum mean glucose of greater than 140 mg/dL, than in those with a maximum blood glucose level of 140 mg/dL or less. Of pa-

tients with maximum blood glu-

cose levels higher than 140 mg/dL, 61 had an infection and 32 did not, whereas those with blood glucose levels of 140 mg/dL comprised 6 with infec-

tion and 51 without. Based on these values, a maximum blood glucose level greater than 140 mg/dL comprised 6 with infec-

tion, and 51 without. Based on these values, a maximum blood glucose level greater than 140 mg/dL comprised 6 with infec-

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tion, and 51 without. Based on these values, a maximum blood glucose level greater than 140 mg/dL comprised 6 with infec-

The mean length of stay was 4 days in the intensive in-

sulin group and 12 days in the control group. “This suggests that there may, in fact, be other changes that are going on getting con-

tributed to its results.

The evidence is somewhat weaker for these specific ques-

However, intensive insulin therapy posi-

tive impact on other outcomes. For example, efforts to opti-

mize glucose control may be considered in patients with milder hyperglycemia, and normoglycemia (plasma glucose between 90 and 140 mg/dL) appears to be a reasonable goal for treatment.

In addition to informing physicians about the importance of hyperglycemia in ACS, the release of the American Heart Association’s scientific statement has another goal, Dr. Deedwania said.

“Although it’s still uncertain whether hyperglycemia is a clear predictor of poor outcome, but many eviden-

ce suggests that hyperglycemia may be a marker or a mediator of adverse out-

comes. The most pressing unanswered ques-

tion, according to Dr. Deedwania, is to determine which treatment for hyper-

glycemia has the best combination of efficacy and safety. One large recent trial demonstrated that hypoglycemia can be more dangerous than hyper-

A critical care physician at the University of Michigan, Ann Arbor, conducted a study to determine whether persistent hyperglycemia during ACS hospitalization has a greater impact on prognosis than does admission hyper-

glycemia alone, whether there is a critical period of vulnerability from hyperglycemia in these patients, whether the best target glucose levels differ in patients with and without pre-

existing diabetes, and what the optimal timing of therapy might be.

Meanwhile, the writing group de-

termined that there is excellent (level A) evidence available to recommend that glucose levels should be part of the initial laboratory evaluation in all pa-

tients with suspected or confirmed ACS. And there is good (level B) evi-

dence that glucose levels should be monitored closely in patients with ACS admis-

eted to an ICU, that it’s reasonable to consider treatment in patients with high levels of hyperglycemia, that in-

sulin by intravenous infusion is the most effective measure to control glu-

cose in ICU patients, and that special at-

tention should be paid to ACS patients with hyperglycemia but no prior history of diabetes.

The evidence is somewhat weaker (level C) for other recommendations. For example, efforts to opti-

mize glucose control may be considered in patients with milder hyperglycemia, and normoglycemia (plasma glucose between 90 and 140 mg/dL) appears to be a reasonable goal for treatment.

In addition to informing physicians about the importance of hyperglycemia in ACS, the release of the American Heart Association’s scientific statement has another goal, Dr. Deedwania said.

“This is a call to action for all the differ-

ten agencies, such as the National Insti-
tutes of Health, to consider doing trials on some of these very specific ques-
tions. This should be a priority.”

DATA WATCH

Top 10 Emergency Department Diagnoses Resulting in Hospital Stays

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of ED Visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>433,500</td>
</tr>
<tr>
<td>Heart failure</td>
<td>396,600</td>
</tr>
<tr>
<td>Nonspecific chest pain</td>
<td>344,500</td>
</tr>
<tr>
<td>Heart attack</td>
<td>223,600</td>
</tr>
<tr>
<td>COPD and bronchiectasis</td>
<td>222,100</td>
</tr>
<tr>
<td>Irregular heartbeat</td>
<td>220,100</td>
</tr>
<tr>
<td>Coronary atherosclerosis</td>
<td>217,800</td>
</tr>
<tr>
<td>Stroke</td>
<td>216,500</td>
</tr>
<tr>
<td>Infection of the blood</td>
<td>210,100</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>181,700</td>
</tr>
</tbody>
</table>

Note: Based on the principal diagnosis on the inpatient record for 23 states in 2005.

Source: Healthcare Cost and Utilization Project
Preemie Asthma Tied to Mom’s Chorioamnionitis

BY MITCHEL L. ZOLER
Elsevier Global Medical News

PHILADELPHIA — Children born prematurely to mothers who developed chorioamnionitis during pregnancy were about fourfold more likely to develop asthma and wheezing during the first 2 years of life, compared with term infants born to mothers without chorioamnionitis, based on data collected on nearly 1,100 children.

The finding needs to be extended by following the children to an older age and by studying other populations if the findings are confirmed in such studies, earlier treatment and resolution of chorioamnionitis may have important implications for the future respiratory health of affected children, Dr. Rajesh Kumar said at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

‘A lot of the chorioamnionitis was subclinical. We don’t know if treatment will prevent the effect of chorioamnionitis on recurrent wheezing, but this would be an area for future study,” Dr. Kumar said in an interview.

“What was surprising was the degree of association that chorioamnionitis had with wheezing and asthma,” whereas no link was seen between prematurity, chorioamnionitis, and food allergy or eczema, said Dr. Kumar, a pediatric allergy and asthma specialist at Children’s Memorial Hospital and Northwestern University, both in Chicago. Ateopy does not appear to play a role in the association.

An alternative, physiological explanation is that chorioamnionitis produces a strong, proinflammatory response that boosts levels of various cytokines, such as tumor necrosis factor-α, and interleukins 6 and 8. Cytokines like these may trigger premature birth, and may also lead to chronic respiratory disease in the fetus.

Results from some prior studies had shown a link between prematurity and an increased risk for asthma, but this link was not confirmed in all studies. Prior studies did not consider the underlying pathogenesis that led to premature birth, which may account for the inconsistency, Dr. Kumar said.

His analysis was based on data from children in the Boston Birth Cohort, an ongoing study at Boston Medical Center that began in 1998. Included were 771 term and 325 preterm infants who completed at least one postnatal examination. These completed numbers make the analysis one of the few prospective studies large enough to allow stratification of the infants in groups according to the severity of prematurity and the presence of chorioamnionitis, he noted.

The average age of the children at their last follow-up visit was 2.2 years. The analysis adjusted for several infant and maternal variables, including breastfeeding, postnatal passive smoking, maternal smoking during pregnancy, and maternal educational status. Infants born at less than 33 weeks gestation to mothers who had chorioamnionitis were 4.0-fold more likely to wheeze and 4.4-fold more likely to have asthma, compared with infants born at 37 weeks or beyond to mothers without chorioamnionitis. (See box.) Both differences were highly significant. In contrast, infants born before 33 weeks to mothers without chorioamnionitis were 2.7-fold more likely to wheeze (a significant difference) but were no more likely to have asthma than those born term infants.

“One of the major issues in our study was that our primary outcome was recurrent wheezing of early childhood. We also evaluated physician-diagnosed asthma, but this is a bit less clear of a diagnosis at a young age. We will continue to follow these children [until] they are 6 years of age to see if the effects of chorioamnionitis on physician-diagnosed asthma will truly equate to persistent asthma by the time the children are older,” Dr. Kumar said.

The associations were even stronger in infants born to African American mothers, who made up about 62% of the study cohort.

Asthmatic Children Bear the Brunt of the Influenza Burden

BY ELIZABETH MECHECATE
Elsevier Global Medical News

The influenza-related hospitalization rates for young children with asthma were four times greater than those of children without asthma, and outpatient visits attributable to influenza were about twice as likely among those with asthma, according to Dr. E. Kathryn Miller and her associates.

The results are similar to those of reviews that found that the rate of influenza-attributable outpatient visits for children with asthma and other medical conditions was higher than among healthy children, the investigators noted. But they added that their study may be the first to use prospective, laboratory-confirmed surveillance over several years to estimate rates of influenza-attributable visits for these two groups of children (Pediatrics 2008;121:1-8).

The investigators conducted a prospective study that included children aged 6-23 months. Patients were either hospitalized between 2000 and 2004 or presented to clinics or emergency departments with acute respiratory illnesses (ARIs) or fever during two flu seasons between 2002 and 2004. In both the hospital and outpatient settings, throat and nasal swabs were obtained and tested for influenza, said Dr. Miller of the department of pediatrics at Vanderbilt University in Nashville, Tenn.

Of the 1,468 children hospitalized, 81 (6%) had lab-confirmed influenza; about one-quarter of these 81 children had asthma. Among children aged 6-23 months, the average annual rate of hospitalizations attributable to influenza was 2.8 cases/1,000 children with asthma, compared with 0.6 cases/1,000 children among healthy children, a significant difference. But the difference was not significant among those children aged 24-59 months: 0.6 cases/1,000 children among those with asthma, vs. 0.2 cases/1,000 children among the healthy children.

Among the 1,432 children enrolled in the outpatient settings, influenza was confirmed in 249 patients (17%); 15% had asthma. Among the children aged 6-23 months with asthma, the average annual rate of outpatient visits attributable to influenza was 316/1,000 children, compared with 152/1,000 children among healthy children; asthma, a significant difference. Among those children aged 24-59 months, the rates were 0.6 cases/1,000 children among those with asthma, vs. 0.2 cases/1,000 children among the healthy children.

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Vaccination rates were 27% in the asthma group and 12%-15% in children without asthma, according to parent reports.
Necrotizing Pneumonia on the Rise in Children

BY DAMIAN MCNAMARA
Elsevier Global Medical News

FORT LAUDERDALE, Fla. — More children with pneumonia are developing necrotizing pneumonia from a growing variety of infectious agents, including methicillin-resistant Staphylococcus aureus, according to a representative, 15-year study.

“Necrotizing pneumonia is real,” Dr. Andrew Colin said. If a child has a persistent fever that does not respond to treatment for 3 or more weeks, along with pleural effusions suggesting community-acquired pneumonia, consider coexisting necrotizing pneumonia, he said.

Multiple organisms are playing a role, indicating a lot of necrotizing pneumonias where we do not know the organism. These could be mycoplasma,” said Dr. Colin, director of the division of pediatric pulmonology, Holtz Children’s Hospital at the University of Miami/Jackson Memorial Medical Center in Florida.

Of 80 patients, a total of 38 (48%) had positive cultures. Streplococcus pneumonia was the predominant organism, although in the more recent years there was a variety of organisms responsible, most notably methicillin-resistant Staphylococcus aureus (MRSA). Dr. Colin said at a pediatric pulmonology meeting sponsored by the American College of Chest Physicians.

Dr. Colin, along with Dr. Gregory Sawicki (the study’s lead author) and associates, found an increasing incidence of necrotizing pneumonia from January 1990 to February 2005 at Children’s Hospital Boston (Eur. Respir. J. 2008 Jan. 23 [Epub ahead of print]). Of 80 cases identified, there was 1 case during 1993-1994; 11 each during 1995-1996 and 1997-1998; 17 cases during 1999-2000; and 12 cases during 2001-2002.

“By the end of the study, years 2003-2004, we had 28 cases in one hospital, which is quite significant,” Dr. Colin said. A meeting attendee asked if children at greater risk for necrotizing pneumonia can be identified.

We don’t have large enough numbers to predict who will develop necrotizing pneumonia,” responded Dr. Colin, who is also professor of pediatrics at the University of Miami. Necrotizing pneumonia presents with coexisting effusion in a majority of patients. In the study, 69 children (86%) had pleural effusion with a low pH (mean 7.08).

It is clinically challenging to differentiate the signs and symptoms of necrotizing pneumonia from the effusion, Dr. Colin said.

Computed tomography with contrast is the best way to diagnose necrotizing pneumonia, Dr. Colin said. The imaging detects the characteristic features, the liquefaction and caviation of lung tissue. Look for demarcation between lung and liquid lung, he suggested.

How to differentiate a lung abscess from liquid in the lung on the imaging was another meeting attendee question. “The differential diagnosis is absolutely critical,” Dr. Colin said. On the CT scan, abscesses appear with thick walls, whereas necrotizing lungs have thin walls and will collapse in a couple of days, he replied. Also, “if you tap the two, the abscess will be positive in culture, the necrotizing lung will be negative.” Although the lungs are often sterile with necrotizing pneumonia, “there are some bad bugs, so everyone gives antibiotics just in case.”

Dr. Colin advocated a conservative approach to prolonged chest tube drainage in patients who develop necrotizing pneumonia. In another of his studies, five of nine children with the condition developed bronchopleural fistula after chest tube placement (Pediatr. Radiol. 1999;29: 87-91).

Three of these children had a surgical chest tube placed for an average of 7 weeks to treat persistent pneumothorax. The longer drainage continues, the greater the risk of puncturing a lung. A bronchopleural fistula is a serious complication that can substantially lengthen a hospital stay and recovery time, he added.

“Despite the serious morbidity, massive parenchymal damage, and prolonged hospitalizations, long-term outcome following necrotizing pneumonia is excellent,” Dr. Colin and his coauthors wrote. In fact, all patients in the study had a complete clinical resolution within 2 months, he added.

“The good news is you do not have to resect damaged lungs—these young patients have a remarkable ability to recover.”

Catheter Drainage Lowered Reintervention Rates

BY DAMIAN MCNAMARA
Elsevier Global Medical News

FORT LAUDERDALE, Fla. — Image-guided catheter placement significantly reduced the need for reintervention among children with parapneumonic effusion, compared with needle aspiration alone, according to Dr. Andrew Colin.

“What we are looking for are predictors, something that can help us. We want markers in the pleural fluid that will predict outcomes,” said Dr. Colin, director of the division of pediatric pulmonology, Holtz Children’s Hospital at the University of Miami/Jackson Memorial Medical Center in Florida.

In a retrospective study, Dr. Colin, lead author Ragheed K. Mitri, and their associates reviewed the medical records, microbial reports, and x-rays of 67 pediatric patients over 5 years (Pediatrics 2002;110: e37). A total of 34 children with effusion had aspiration drainage, while 33 others had percutaneous “pigtail” catheters placed.

Median lengths of hospital stay and complication rates were similar between groups. The primary outcome was a need for reintervention, which occurred in 18 children (27%).

“We found three significant predictors of reintervention,” Dr. Colin said at a pediatric pulmonology meeting sponsored by the American College of Chest Physicians.

Children in the aspiration-only drainage group experienced significantly higher reintervention rates. Use of image-guided needle aspiration was associated with a more complicated outcome, vs. image-guided percutaneous catheter drainage (odds ratio, 8.0).

“The second predictor we came up with was pH, as much as the literature predicted,” Dr. Colin said. Reintervention was more likely with a pH of less than 7.0 vs. greater than 7.0 (OR, 14.3). “If you have a low pH, things are not likely to be good. A pH of 7 is actually quite low compared to the general population.”

Glucose was not an independent predictor of bad outcome but had predictive value in conjunction with lower pH. Dr. Colin said. “If your pH is over 7.2, glucose does not matter as much, because you are unlikely to do an intervention anyway.

However, with pH below 7.0 and glucose below 20 mg/dL, a reintervention is required about 75% of the time. "And you should probably do it earlier rather than later," Dr. Colin noted.

Timing is critical, because the effusion can change over time. Intervention is easier during the initial, free-flow phase of parapneumonic exudate. After a period of 48-72 hours, the effusion often becomes more viscous. This is called the fibropulent phase, during which fibrin accumulates and abundant loculation occurs, Dr. Colin explained.

“So, you have a limited time to intervene—a matter of hours in some cases.”

The gel-like substance can continue to progress to a third, organizing phase, with increased fibroblast activity.

Loculation of fluid was the third predictor in the study.

“When with loculation on the ultrasound, there is an odds ratio of 3.6 that you will have to go back to that chest,” said Dr. Colin, who is also professor of pediatrics at the University of Miami.

Therefore, primary catheter placement for parapneumonic effusions should be considered in children who undergo diagnostic thoracentesis. Dr. Colin said. Because of the associations they found, an on-site pH meter and a glucometer could facilitate the tube placement decision.

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Aggressive Surgery Improved Outcomes in MDR-TB

Keystone, Colo. — Aggressive resectional surgery has led to markedly improved microbiologic and clinical success in treating multidrug-resistant pulmonary tuberculosis, according to experience with patients at the National Jewish Medical and Research Center in Denver.

The use of surgery to treat MDR-TB patients at the center is associated with a greater than fourfold increased likelihood of an initial favorable response to treatment. Fluoroquinolone therapy also is predictive of an initial favorable response, but only in patients older than 40 years.

“Surgery has become a very significant part of our practice at National Jewish,” said Dr. Charles L. Daley, head of the division of mycobacterial and respiratory infections at the center. “We think that in select patients, surgical resection is really important to consider.”

The goal of the surgery is to remove cavitary lesions and sections of destroyed lung with a high bacillary burden. The operation is most likely to be successful in patients with focal disease and adequate pulmonary function, said Dr. Daley at a meeting on allergy and respiratory disease sponsored by the National Jewish Medical and Research Center.

Good surgical candidates are patients with MDR-TB who remain culture-positive after 4-6 months of drug therapy, as well as patients with extensively drug-resistant TB (XDR-TB). The World Health Organization’s revised definition of XDR-TB issued in late 2006 describes it as MDR—that is, resistance to at least isoniazid and rifampin—plus resistance to any fluoroquinolone and one of the second-line injectable drugs, namely amikacin, capreomycin, or kanamycin.

The success of the surgical strategy was shown by a retrospective study published in 2004. The study reviewed outcomes in 205 patients with MDR-TB treated at National Jewish during 1984-1998, and compared the outcomes with those of 171 other MDR patients treated there during 1973-1983. All the MDR patients in the review were severely resistant to a median of six TB drugs and treated with a median of six agents while at National Jewish. Treatment outcomes were better in the more recent cohort. Analysis identified two major reasons why: resectional surgery and fluoroquinolone therapy. These were the two novel elements of MDR-TB management introduced at the center after 1983. Each was an independent predictor of good outcome in the study, said Dr. Daley, who also is a professor of medicine at the University of Colorado, Denver.

The initial favorable response rate, defined as at least three consecutive negative sputum cultures over at least 3 months, was 65% in the 1973-1983 cohort, compared with 85% in those treated during 1984-1998. The overall cure rate improved from 56% in 1973-1983 to 75% afterward. Moreover, the TB death rate fell from 22% to 12%.

In a multivariate analysis, surgery was associated with a 4.6-fold increased likelihood of an initial favorable response to treatment. Fluoroquinolone therapy was associated with a 4.1-fold increased likelihood of an initial favorable response to treatment, but only in patients older than 40 years.
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Fluoroquinolone therapy, introduced in the 1980s, was also predictive of an initial favorable response but only in patients more than 40 years old. There was a trend toward improved survival in patients who underwent resection. It didn’t reach significance, perhaps because of the relatively small sample size (Am. J. Respir. Crit. Care Med. 2004;169:1103-9).

The use of surgical resection climbed steadily at National Jewish over the study years as physicians came to recognize that it resulted in improved outcomes and had a low complication rate. Just 4% of patients treated for MDR from 1973-1983 underwent one or more resectional procedures, compared with 44% discharged in 1984-1988, 63% in 1989-1993, and 83% in 1994-1998.

“This surgery should be performed by experienced surgeons,” Dr. Daley stressed. “We used to use a thoracotomy but are now turning to VATS (video-assisted thoracoscopic surgical) resection whenever possible,” he said.

Based upon numerous published studies, the predictors of therapeutic failure in patients with MDR-TB include a low body mass index, comorbid HIV, previous therapy, and poor adherence, according to Dr. Daley.

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Blood-Related Transfusion Issues: A Significantly Higher Rate in Older Adults

Dr. Philip Marcus, FCP, comments:
These findings support the need for transfusion risk assessment and give weight to a widely held belief about transfused blood, i.e., the newer the better.
Old blood can be thought of as “bad blood.”
Although this study involved only those patients undergoing coronary and heart valve surgery, the findings may be applicable to other populations, as well.
CMS Adds Patient Satisfaction to Hospital Web Site

BY JOYCE FRIEDEN
Elsevier Global Medical News

Arlington, Va. — Now that the Centers for Medicare and Medicaid Services has added patient satisfaction data to its Hospital Compare Web site, patients will have more to consider when they decide which hospital to use for an elective procedure.

The Web site already included hospital-specific information on clinical measures, such as antibiotic prophylaxis before surgery and aspirin upon admission for a heart attack. New patient satisfaction data include items such as nurse communication and hospital room cleanliness.

“This is like Travelocity for health care,” said Health and Human Services Secretary Mike Leavitt. “When people have information and hospital room cleanliness, they have the choice, they make good choices.” Mr. Leavitt spoke at the annual meeting of the Association of Health Care Journalists.

The patient satisfaction data come from the Consumer Assessment of Healthcare Providers and Systems, a survey administered by 2,500 hospitals to patients discharged between October 2006 and June 2007. The survey included 27 questions about patients’ hospital experience, including communication with doctors and nurses, responsiveness of hospital staff, cleanliness and quietness of the hospital environment, and pain management.

The database also will include the volume of certain elective procedures provided at the hospital as well as what Medicare pays for those procedures.

The Centers for Medicare and Medicaid Services (CMS) Deputy Administrator Herb Kuhn said the information will be valuable even if patients already have selected a hospital for an elective procedure.

“There are three reasons people pick a hospital,” he said in an interview after Mr. Leavitt spoke. “They heard it was good, it’s where their physician spends a lot of his time, or it’s convenient to them. We want to add another dimension here for people to understand. Okay, if that’s where you’re going, what do you know about this place?”

The database also will be a good motivator for hospital improvement, Mr. Leavitt said. “Wherever in health care there’s robust information about quality and cost, the cost goes down and the quality goes up,” he said.

Mr. Leavitt stressed that CMS was not posting the data in order to punish hospitals that aren’t performing well, but to add another dimension for people to understand:

“This is not about eliminating anyone; it’s about improving everyone,” he said. “The minute a provider sees that they are at lower quality than the marketplace requires, they improve.”

As for whether those hospitals that don’t improve might eventually face consequences, “they improve.”

Without consumers and regulators and others having a means of measurement, we continue to reward mediocre—and in some cases, poor—performance.

While this is not about eliminating hospitals that are not performing well, we should certainly not assume that the poor performers will not be eliminated, either by the marketplace or by those who oversee quality,” Mr. Leavitt explained.

But it’s not only hospitals and patients who can use the new data, according to Gerald Shea, assistant to the president for governmental affairs at the AFL-CIO.

“This is important for physicians and other clinicians,” he said at the meeting. “We hope physicians take this information and make it part of their regular, routine discussions with their patients.”

### Data Watch

Top 10 Diagnoses for Discharges From Short-Stay Hospitals (in thousands)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart disease</td>
<td>19,747</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13,460</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9,150</td>
</tr>
<tr>
<td>Psychoses</td>
<td>4,154</td>
</tr>
<tr>
<td>Mothers with deliveries</td>
<td>4,038</td>
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<tr>
<td>Anemias</td>
<td>3,831</td>
</tr>
<tr>
<td>Malignant neoplasms</td>
<td>3,439</td>
</tr>
<tr>
<td>Volume depletion</td>
<td>2,058</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2,385</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2,230</td>
</tr>
</tbody>
</table>

Source: Centers for Disease Control and Prevention

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### Education Calendar

**American College of Chest Physicians 2008**

**May 9 - 10, 2008**

The Northeast Regional COPD Conference
Bolton Landing, New York

**June 22 - 24, 2008**

International Conference on Chronic Ventilated Patients
Tel Aviv, Israel

**July 9 - 11, 2008**

Updates in Pulmonary Medicine
Cairo, Egypt

**August 6 - 9, 2008**

10th Anniversary International Meeting on Respiratory Care
Indonesia

**August 7 - 10, 2008**

Heart, Lung & Critical Care Congress 2008
Hyderabad, India

**August 22 - 25, 2008**

ACCP Sleep Medicine Board Review Course
Orlando, Florida

**August 22 - 26, 2008**

ACCP Critical Care Board Review Course
Orlando, Florida

**August 27 - 31, 2008**

ACCP Pulmonary Board Review Course
Orlando, Florida

**October 25 - 30, 2008**

CHEST 2008
Philadelphia, Pennsylvania

**Future CHEST Meeting Dates**

**October 31 - November 5, 2009**

CHEST 2009
San Diego, California

**October 30 - November 4, 2010**

CHEST 2010
Vancouver, BC, Canada

**October 22 - 27, 2011**

CHEST 2011
Honolulu, Hawaii

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**Practice Trends**
Too Much, Too Little Sleep Doubles Death Risk

BY BRUCE JANCIN
Elsevier Global Medical News

COLORADO SPRINGS — Change in sleep duration during midlife is associated in a U-shaped fashion with risk for death more than a decade later. Dr. Francesco Cappuccio reported at a conference of the American Heart Association.

The major driver of increased mortality among individuals at the low end of the sleep duration continuum is an excess of cardiovascular deaths, while in long sleepers, the increase in mortality is due to noncardiovascular causes, according to the results of the Whitehall II study, said Dr. Cappuccio of Warwick Medical School, Coventry, England.

Whitehall II is a prospective cohort study of 10,308 white-collar British civil servants who were 35–55 years old when enrolled in the study in 1985-1988. Because work, parenthood, and other demands on time make sleep deprivation pervasive in contemporary society, Dr. Cappuccio and his coworkers decided to study whether lack of sleep carries a price.

The Whitehall II analysis of the impact of changes in sleep duration included information on baseline sleep patterns in 7,729 participants and changes in those patterns over the next 5 years. Participants then were followed for mortality through 2004.

Cardiovascular mortality was 2.4-fold higher among subjects who slept an average of 6-8 hr/night at baseline but cut their sleep duration to 5 hr/night or less over the next 5 years follow-up, compared with those who held fast to the 6- to 8-hour pattern. The findings held after adjustment for potential confounding factors including age, employment grade, marital status, blood pressure, body mass index, alcohol intake, smoking status, comorbid illness, and physical activity.

In those who increased their sleep duration from 7-8 hr/night at baseline to 9 or more, there was an adjusted 2.1-fold increase in noncardiovascular mortality.

Short sleep duration is known to be associated with hypertension, weight gain, and diabetes, all of which increase cardiovascular risk. In contrast, the mechanism for the relationship between long sleep and increased mortality is unclear. Hypotheses include potentially significant links with depression and cancer-related fatigue, added Dr. Cappuccio.

SLEEP-DISORDERED BREATHING MORE COMMON IN OBESE INPATIENTS

BY LEANNE SULLIVAN
Elsevier Global Medical News

Sleep-disordered breathing in hospitalized patients is more common in those who are obese and those who have heart failure. Of the 94 patients in the treated group who normalized their sleep apnea (defined as complete or almost complete cessation of airflow—less than 25% of baseline—lasting 10 seconds or longer), and hypopnea (defined as a fall in oxygen saturation of at least 4% or an arousal from sleep). An apnea-hypopnea index (AHI) greater than 10 was classified as sleep-disordered breathing (J. Clin. Sleep Med. 2008;4:105-10). Of the 94 patients, 77% had sleep-disordered breathing, and of those with the condition, 95% had obstructive sleep apnea.

The posttreatment polysomnography, however, indicated some significant improvements in the treated group, compared with controls. In fact, 21 out of the 24 patients in the treated group normalized their sleep apnea, Dr. Gozal said. The treatment group showed significant improvements in oxygen saturation (95.5% vs. 89.3%), and in respiratory arousal index (0.8 per hour of TST). No significant changes were seen over time in the control group children.

Although randomized, double-blind, placebo-controlled trials are needed to confirm the current findings, the present study clearly establishes the beneficial role of anti-inflammatory approaches for asymptomatic children with mild sleep-disordered breathing after T&A, Dr. Gozal said.

Dr. Gozal disclosed he is on the national speakers bureau for Merck & Co., which manufactures montelukast.

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Researched
Mechanical ventilation for patients with respiratory failure can induce or exacerbate lung injury, presumably through high shear forces generated from overdistention and cyclic opening and closing of lung units. Research in animal models and clinical studies of patients with asthma and acute lung injury (ALI) undergoing mechanical ventilation have demonstrated that a strategy of low tidal ventilation with positive end-expiratory pressure (PEEP) can attenuate the lung injury induced by the ventilator and improve clinical outcomes (N Engl J Med 2000; 342:1301). In addition, there are some data suggesting that a reduction in tidal volume in all patients with respiratory failure may reduce the risk of ventilator-associated lung injury (Gajic et al. Crit Care Med 2004; 32:1817).

A necessary consequence of this approach is some degree of hypoventilation, which leads to hypercapnia and respiratory acidosis. Given the widespread use of protective ventilatory strategies while tolerating respiratory acidosis (an approach termed “controlled hypoventilation” or “permissive hypercapnic”), understanding the effects and management of respiratory acidosis is essential. Case series and clinical studies have suggested that hypoventilation and moderate respiratory acidosis can be well tolerated in patients with respiratory failure (N Engl J Med 2000; 342:1301; Gajic et al. Crit Care Med 2004; 32:1817), although the exact cut-off of an acceptable arterial pH or CO2 has not been determined.

Fortunately, there is very little to guide us in terms of randomized controlled trials; thus, defining a “safe” pH and CO2 will depend, in part, on the characteristics of the patient’s illness (i.e., hemodynamic stability, arrhythmias, cerebral edema, etc.) as well as the clinical judgment of the care team.

In a landmark study (Hickling et al. Crit Care Med 1994; 22:1568), the authors demonstrated a relatively low mortality rate (26%) in patients with ARDS ventilated with low tidal volumes. These patients had a mean arterial CO2 of 67 mm Hg and a mean pH of 7.23 without parent adverse outcomes. However, it should be noted that hypercapnia and respiratory acidosis can lead to arrhythmias, cardiac depression, pulmonary hypertension, prolonged weakness, and increased cerebral blood flow, and may raise intracranial pressure. Fortunately, these changes are largely attenuated when there is a gradual development of acidosis (Hassett and Laffey. Crit Care Med 2007; 35:2229).

In addition, patients managed with controlled hypoventilation often require fairly high doses of potent sedatives in order to tolerate the discomfort of a respiratory acidosis, and, thus, may have an increased risk of complications related to increased sedation. These data suggest that although it appears that hypercapnic acidosis can be well tolerated, in theory, there could be some point where the benefits of controlled hypoventilation are outweighed by adverse effects of respiratory acidosis.

Despite the potential complications of hypercarbic acidosis, research in animal models has suggested that respiratory acidosis and hypercapnia may actually have beneficial effects in the setting of ventilator-induced lung injury, sepsis, ischemia-reperfusion injury, and shock (Hassett and Laffey. Crit Care Med 2007; 35:2229).

In addition, on the cellular level, respiratory acidosis may attenuate cytokine release, free radical production, capillary permeability, and lactic acidosis (Ni Chonghaile et al. Curr Opin Crit Care 2005; 11:56). These beneficial effects are thought to be related to the acidosis, although there may be some additional benefit from hypercapnia. However, more recent research has suggested that hypercapnia can lead to alveolar epithelial cell dysfunction and, thus, may also have detrimental effects in respiratory failure (Vadasz et al. J Clin Invest 2008; 118:752). Recent secondary analysis of patients in the ARDS network study has demonstrated reduced mortality in patients with hypercapnic acidosis, only in the group ventilated with large (12 mL/kg) tidal volumes (Kregenow et al. Crit Care Med 2006; 34:1).

Although these data suggest a potentially clinically relevant benefit for respiratory acidosis, there are no definitive data comparing the effects of hypercapnic respiratory acidosis on outcomes independent of the levels of lung stress. Thus, it is unclear whether respiratory acidosis is truly beneficial in the management of patients with respiratory failure, independent of the ventilatory strategy used.

The data do suggest, however, that when carefully applied, controlled hypoventilation with respiratory acidosis can be well tolerated and used without serious adverse events.

**Editor’s Note**

Dr. Benjamin D. Medoff
Assistant Professor of Medicine
Center for Immunology and Inflammatory Diseases
Pulmonary and Critical Care Unit
Massachusetts General Hospital
Boston, MA

Watch for Part 2 on this topic in the June issue of CHEST PHYSICIAN.
PRESIDENT’S REPORT

Capitol Hill Caucus: Reaffirming the Need for Our Involvement

I attended the ACCP 15th Annual Capitol Hill Caucus in early April. It was a wonderful event. There were more than 75 attendees (in past years, 40 to 50 attendees was considered a good year). Twenty-eight attendees were ACCP Governors (37%) and 26 were at-large attendees (35%). Some of our sister organizations were also represented by our members and attendees, including the ATS, NAMDR, AACN (American Association of Critical-Care Nurses), and the Alpha-1 Foundation.

The discussions the first day, as well as during our Capitol Hill visits to our congressmen, were focused on four primary issues:

- Pulmonary rehabilitation legislation
- The critical care workforce crisis
- Medicare physician payment reform
- The Family Asthma Act

Day 1—Morning: Attendees were updated on the primary issues of each bill. As part of that discussion, one of the attendees was asked to give a personal patient-related vignette that was illustrative of the need and practical impact of each bill. This was done so that each attendee could get a feel for how important such vignettes are when addressing the congressmen. The need and importance for each piece of legislation is so much more urgent when we relate it to personal experiences and impact on our patients.

I was asked to give a patient example of the need for the Family Asthma Act. It is a bill initiated by Senator Hillary Clinton (with direct consultative input by ACCP member Dr. Irwin Berlin, FCCP) that would provide federal support for innovative interventions (grants), particularly in underserved patient communities, that would help prevent and control asthma and improve patient self-management of the disease.

The example I gave was an adult asthma patient who lives in the southeast area of DC, an area where asthma per capita health statistics are among the worst in the country. She had an acute asthma attack but did not feel confident about going to local acute care facilities (especially after the closure of DC General Hospital several years ago and the financial and health delivery challenges of the local acute care facilities). She, therefore, did not call 911 for an ambulance but, instead, took two city buses to our facility (Howard). There, she walked into the ED, collapsed, was intubated, mechanical ventilation was initiated, and she was admitted to our medical ICU. She survived to tell the story!

Such a story is indicative of the great disparities in care throughout our country and the particular disparities in asthma care. It is the kind of story that resonates with our congressmen. A bill such as the Family Asthma Act is essential if we are to begin to close the disparity gap.

Day 1—Afternoon: Several of our attendees engaged in role playing with former Representative Jim Davis (now employed by our legislative counsel in DC, Holland & Knight). It was quite effective. Selected attendees were asked to model a congressional visit on each of the four bills with Mr. Davis, who was tough and effective in his role of a congressman! The presentations were critiqued by both the audience and Mr. Davis. It was an excellent example and teaching tool for our congressional visits the next day.

Day 2—Morning and afternoon: A briefing was held by several congressmen and senators (bipartisan representation of Republicans and Democrats) on the status of the four bills in Congress. The speakers included four physicians. The presentations were quite interesting and helpful. Next, we visited Capitol Hill (Senate and House of Representatives offices), where we each interacted with our local congressmen and senators (in most cases their legislative aides). We were expected to lobby on each of the four bills and reiterate our support for FDA regulation of tobacco.

Day 2—Evening: We met back at the hotel to relate our experiences of the afternoon, the results of which were generally diverse. Some congressmen were quite supportive of almost all bills and FDA tobacco regulation. Others were not as supportive of the tobacco issue or knowledgeable about the critical care workforce issue or pulmonary rehabilitation. Most were supportive of Medicare physician payment reform, and they accepted the fact that the SGR (sustainable growth rate) is flawed but were inclined to continue delay of a true solution to the SGR problem. Virtually all congressmen were unaware of the Family Asthma Act. Much work needs to be done on this issue if the bill is to be considered and passed.

In summary, the caucus this year was well-organized, stimulating, and informative. It served as a reaffirmation for me of the need for all of us, as physicians, to take our heads out of the sand and get more involved in providing information and feedback to our government representatives, especially at the local, grassroots level. The stakes are high, especially in a year when health-related issues are so central to our national political discourse. Get involved! Contact your local ACCP Governor for help or the ACCP Government Relations Committee staff (Lynne Marcus at lmarcus@chestnet.org). Your input and involvement are essential.

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Product of the Month: Web Updates on ICU Hypertensive Crises, Pneumonias

View the newest ACCP educational products available online, which feature information from CHEST. 2807 satellite symposia. The information also was published as supplements accompanying the April issue of CHEST PHYSICIAN.

- Clinical Challenges and Case Studies of Microorganisms in Pneumonias—Addresses the challenging issues surrounding the recognition and management of pneumonia. Infectious disease specialists offer their insight into current issues and standards related to bacterial pneumonia. Clinicians involved in the care of patients with pneumonia will find the information timely and readily applicable to clinical practice.
- Hypertensive Crises in the Critical Care Setting: Current Perspectives and Practice Challenges—A review of hypertensive emergencies, which includes a spectrum of clinical syndromes and a focus on specific drugs and therapeutic strategies available in the ICU.
This year’s Sleep in America Poll evaluates sleep habits and productivity in the workplace. Results from this large and increasingly high-profile poll were made available to the public during National Sleep Awareness Week, which is traditionally the first week of March. Continuing our tradition of partnering with the National Sleep Foundation (NSF) on important aspects of sleep health, the ACCP Sleep Institute Steering Committee worked with NSF to develop an echo poll (a separate poll that asks similar questions as the “parent” poll but to a different and usually smaller audience) that assessed the sleep habits and work productivity of ACCP members.

Methods
A task force of the ACCP Sleep Institute Steering Committee developed the questions used for the echo poll. The poll consisted of 30 multiple response questions and one open-ended comment section. The poll, which was administered through the ACCP Web site via an online survey tool, was sent to 5,006 randomly selected US ACCP physician members. In order to maximize the response rate, requests for responses were sent out at weekly intervals, three times, from December 17, 2007, to January 3, 2008. The goal of our poll was to “echo” the NSF’s Sleep in America Poll, in that, when possible, the responses of the physician population were compared with those obtained by the Sleep in America Poll.

FCCP Responses
There were 181 responses (12.1%) by the time the poll ended on January 7, 2008. Of the respondents, 73.6% were male, 2.3% were African-American, 6.3% were Hispanic, and 13.9% were Asian. Married or partnered respondents account for 84.3% were ACCP members for at least 6 years (range 6 to >20 years), and 87.8% were in medical practice for more than 6 years (range 6 to >20 years). General health was perceived as good, very good, or excellent in 97.9% of respondents. Physician respondents were largely satisfied with their work (79.7% were satisfied or very satisfied) and had mostly positive interactions with others at their workplace (96.8% reported good, very good, or excellent interactions).

Regarding work routines, which were the focus of the poll, most practitioners start their workday between 7:00 AM and 9:00 AM and finish between 5:00 PM and 8:00 PM. Bedtimes and wake-up times did not vary much across workdays and non-workdays. The majority of respondents indicated that their bedtime was between 10:00 PM and midnight. The majority of respondents also indicated that their wake-up time was between 5:00 AM to 7:00 AM on workdays and between 6:00 AM and 9:00 AM on days off. Sleep amounts varied from 6.5 h on work nights and 7.5 h on days off. In contrast to the average physician practice, most physicians claimed that 7 to 8 h of sleep would be optimal. The number of caffeinated beverages consumed by physicians averaged three daily. Most physicians who consumed caffeine saw this as a “habit” (83.3%), rather than a strategy to “keep awake.” Difficulty initiating or maintaining sleep was rare in this population, although almost 30% did not feel refreshed upon awakening. Caffeine use was more common in physicians than the general population (93% vs 82%), although average consumption in those who consumed caffeine was similar (approximately three servings daily). In general, more physicians reported very good to excellent health than the general population (83.6 vs 56.0%).

Comparison With the NSF Poll
Results for physicians and the general population were similar in terms of average reported sleep at night, as well as perceived sleep needs. More physicians responded that work prevented adequate sleep time and that they had missed at least one family event due to sleepiness. Caffeine use was more common in physicians than the general population (93% vs 82%), although average consumption in those who consumed caffeine was similar (approximately three servings daily). In general, more physicians reported very good to excellent health than the general population (83.6 vs 56.0%).

Discussion and Implications
Physicians identify a gap in their perceived sleep needs vs what they obtain on a regular basis. A somewhat longer time in bed on days off supports this perception and is similar to the general population (83.6 vs 56.0%). Physicians may be struggling with sleep deprivation. Despite these limitations, the echo poll provides the ACCP Sleep Institute with a useful snapshot of the ‘state of sleep’ of what is likely a representative group of FCCPs in practices across the country. The take home message is that a significant number of pulmonary physicians (Dare we extrapolate to other physicians?) are modestly sleep-deprived but, nonetheless, seem to get through their days in a satisfactory manner. A minority of subjects seemed to be truly struggling with sleep deprivation. Evidence from recent research over the past 3 years has started to link even relatively modest degrees of chronic sleep deprivation with adverse health, such as weight gain, insulin resistance, and decreases in vigilance. While these research findings should still be considered preliminary, it may not be too early to consider getting adequate sleep. To borrow a slogan from the NSF, sleep is “as important as good nutrition and exercise, only easier.”

This Month in CHEST—Editor’s Picks

- Safety of Long-Acting Beta-Agonists in Stable COPD: A Systematic Review. By Dr. G. J. Rodrigo, et al
- Is Metalloproteinase-7 Specific for Idiopathic Pulmonary Fibrosis? By Dr. J. W. Huh, et al
- A Web-Based Delphi Study on the Interpretation of Chest Radiographs for Patients in ICUs. By Dr. G. Hejblum, et al
- Ventilator Settings and Outcome of Respiratory Failure in Chronic Interstitial Lung Disease. By Dr. E. R. Fernández-Pérez, et al
- Evidence-Based Medicine Has a Sound Scientific Base. By Dr. P. J. Kranias, et al
- Evidence-Based Medicine Lacks a Sound Scientific Basis. By Dr. M. J. Tobin
- Definitive Care for the Critically Ill During a Disaster. From a Task Force for Mass Critical Care Summit Meeting, Jan 26-27, 2007

www.chestjournal.org
Affiliate

By Dr. Kevin Chan, FCCP, NetWork Chair

The American College of Chest Physicians strives to offer health-care providers in the specialties of pulmonary, critical care, cardiology, thoracic surgery, and sleep medicine an avenue for educational and practice resources, opportunities for presentation and discussion of scientific information, and opportunities for leadership. The Affiliate NetWork concentrates these goals toward the fellow-in-training and physicians early in career development. There are currently 2,400 affiliate members of the College who have access to discounts on many educational activities. In addition, the ACCP offers opportunities for publication and presentation specifically for affiliate members.

Activities of participants and affiliate members include the annual pulmonary, critical care, and sleep medicine review courses, ABIM-sanctioned SEP Pulmonary and Critical Care Module reviews, and the ACCP-SEEK pulmonary, critical care, and sleep medicine board preparation courses offered at CHEST. In addition, many affiliate members are benefiting from the hands-on learning experiences provided by the ACCP’s new simulation center. Affiliate members made up 40% of participants at the clinical simulation sessions at CHEST 2007.

The Affiliate NetWork offers members the opportunity to present case reports and scientific abstracts at the annual CHEST meeting. The CHEST Challenge is also spearheaded by the Allied Health NetWork and continues to involve an increasing number of pulmonary and critical care medicine training programs. Each year at the CHEST meeting, fellows in training from various programs compete as teams in live, game-show-style rounds. Responding to membership needs in the area of career development after fellowship, questions on contract negotiations, practice lifestyle, types of practices, and how to find the right job were the focus of new presentations at CHEST 2007. The Affiliate Luncheon presentation by Dr. Michael Nelson, FCCP, Chair of the Private Practice NetWork, Transition From Fellowship to Practice: Picking a Private Practice, was well received. Plans are underway to partner with the Private Practice NetWork to develop a course on choosing a career and finding the right practice. Please visit the newly designed Web pages at www.chestnet.org/networksaffiliate to find out how to become involved with the Affiliate NetWork. We look forward to working with you and with you soon.

Airways Disorders

By Dr. Paula Anderson, FCCP, NetWork Chair

Dr. William Calhoun, FCCP, gave the special presentation at the Airways Disorders NetWork Open Meeting at CHEST 2007 on “Noninvasive Measures of Airways Inflammation.” These measurements can reflect airway inflammation in asthma and include invasive tests (bronchial biopsy and bronchoalveolar lavage), as well as noninvasive tests (induced sputum, exhaled breath analysis, and methacholine or mannitol challenge). To date, these types of tests are not included in asthma clinical practice guidelines as outcomes measures for asthma control, Dr. Calhoun discussed in clinical practice. He summarized that the noninvasive markers lack a “gold standard” of airway inflammation but may be reflective of important asthma outcomes. Several markers have good predictive value for important asthma outcomes, such as the use of induced sputum analysis or exhaled nitric oxide to gauge the need for additional inhaled corticosteroids. Dr. Calhoun also stated that exhaled nitric oxide and mannitol challenge testing are nearing clinical applicability.

Another controversial area in asthma therapy involves safety of long-acting beta2-agonists (LABAs). The US Food and Drug Administration issued a black box warning for LABAs in 2005 based on literature suggesting asthma mortality was increased with LABAs. The Airways Disorders NetWork Steering Committee wanted to investigate whether the black box warning has influenced the practice of specialists and primary care physicians and developed a NetWork project to survey participants about LABA use. A questionnaire was distributed to members of the ACCP the American Academy of Allergy, Asthma and Immunology (AAAAI), the American Academy of Family Practice (AAFP), and the American College of Physicians (ACP).

There were 1,107 physicians who responded. Analysis of the results showed very interesting effects of the black box warning on the different specialties, and a manuscript is now being prepared for publication.

To learn more about the ACCP Airways Disorders NetWork, to get involved, or to suggest a NetWork project, go to www.chestnet.org/networks/airway_disorders/index.php.

Women’s Health

How Does the Tobacco Industry Use Your Office To Promote Smoking?

By Virginia Reichert, NP (Steering Committee Member); Patricia Felan, RN; and Susan Kennedy, LMSW

While you are working to make your patients healthy, tobacco companies are advertising in magazines that your patients read in your waiting room. Advertisements in periodicals are the main avenue that the tobacco industry uses to promote their deadly products. Tobacco advertisements normalize tobacco use, undermine tobacco cessation efforts, and encourage youth initiation. In addition, tobacco company advertising can influence and constrain a magazine’s ability to report on and accurately convey the health consequences of tobacco use.

Two states have created initiatives to educate health-care providers about these advertisements and to encourage them to allow only tobacco ad-free periodicals in their waiting rooms. The Maryland State Medical Society, in collaboration with the Campaign for Tobacco Free Kids® and Smoke Free Baltimore County, asked physicians and health-care organizations to sign endorsement agreements to replace the displays with free displays that had been sent to their offices. Physicians were educated about the “Quit Assist” displays that have been sent to physicians’ offices by Philip Morris. Many physicians were shocked to learn that they were unknowingly displaying these materials in their offices.

On the surface, they seem like a good idea, but the cessation message is a soft sell because it is really a public relations campaign. Providers were asked to replace the displays with free state cessation materials that promoted the NYS Smokers’ Quitline.

Once made aware, most physicians agreed that they would rather not display smoking cessation materials sponsored by tobacco companies and magazines with cigarette ads in their waiting rooms.

For more information on the efforts of the NetWork, visit www.chestnet.org/networks/womens_health/index.php.

Pulmonary Physiology, Function, and Rehabilitation

By Dr. Brian Carlin, FCCP, NetWork Chair

Our NetWork has instituted several changes to its NetWork Web pages at www.chestnet.org/networks/ptfr. These include a section on interesting pulmonary function and cardiopulmonary exercise testing cases, as well as a section on selected up-to-date references in the field.

The NetWork is involved with several important projects. The development of performance measures for pulmonary rehabilitation has been approved and will be designed in a fashion similar to the ACCP/AACVPR/AHA 2007 performance measures in cardiac rehabilitation (Thomas et al. J Cardiopulm Rehabil Prev 2007; 27:260).

The joint ACCP/AACVPR guidelines published in 2007 (Ries et al. Chest 2007; 111 suppl 14: S5) will be used as a basis for this document.

Representatives from the major pulmonary organizations are currently being selected to participate in the process.

The NetWork also participated in a response to the recently released, “Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline from the American College of Physicians,” (Qaseem et al. Ann Intern Med 2007; 147:633). Particular emphasis was placed on the differences between the ACCP/AACVPR/ACCP guidelines for pulmonary rehabilitation and the ACP publication.

Ongoing efforts are underway to promote the congressional bills regarding pulmonary rehabilitation and were addressed during the recent ACCP Capitol Hill Caucus.
**For Whom The CHEST Foundation Serves?**

Over the years, a long list of talented College members (only a few of whom were ancient, past presidents) defined and refined the focus of The Foundation. These foci today are clinical research, critical care/end-of-life care, tobacco prevention education, and humanitarian service. Even while defining these core interests, the Foundation has been able to fund over $1 million in humanitarian awards to support 160 projects worldwide, where ACCP members donate their time and invest more than $1 million in clinical research awards to hundreds of members to promote innovations in patient care! Hundreds of antitobacco educational efforts have been made throughout the country, touching thousands of students’ lives and propagating by training an ever-growing group of teachers, while developing enduring tools for their use. Through our Distinguished Scholar program, we have supported six outstanding investigators whose projects contribute to clinical programs and improvements in critical care, respiratory care, and thrombosis.

Through the sponsorship of the Critical Care Family Assistance Program, now in partnership with the American Association of Critical-Care Nurses, we have improved the experience of hundreds of health professionals and patients in ICUs across the country.

All of this has been accomplished on behalf of the College, in support of its Fellows, its members, and the patients for whom they care. Even these major accomplishments do not completely represent the contributions of The Foundation. Indeed, soon after its inception, it was charged with managing the ACCP’s many honor lectures and awards; endeavoring to better support these financially and to make them consistently relevant to our membership and mission. In addition, The Foundation has been the home for our Pro Bono Committee and its many good works in the occasion of disasters at home and abroad. The Foundation serves as the primary liaison with the Palliative and End-of-Life Care Network and the Women’s Health Network. Each of these naturally fit into one or more of our core missions.

These accomplishments should make it clear that although The Foundation was conceived and, initially, nurtured by a small group of dedicated members and staff, it serves the College as a whole, its members, and the world in which we live and work.

In answer to the title’s question: The Foundation serves for thee, and all who have contributed to these efforts can be proud of the selflessness of your gifts; the extent of your reach. In future issues of CHEST PHYSICIAN, we will examine how The Foundation has begun to respond to these capabilities bequeathed by giving through its four foci, ever striving to fulfill its mission of support for the College.
‘One Wiz With’: Cheesesteaks and CHEST 2008

R
uch in American history, Philadelphia is largely recognized as the birthplace of life, liberty, the pursuit of happiness and cheesesteak. Cheesesteaks made their debut in South Philadelphia in 1930. Today, a trip to Philly isn’t complete unless you’ve had at least one of these famed sandwiches. Here are a few tips to help you enjoy a cheesesteak during CHEST 2008.

First, you should know how to order. The idea is to let the cook know (a) you want a cheesesteak, (b) the type of cheese you want—Cheez Whiz®, American, or provolone, and (c) whether or not you want fried onions. Be as concise as possible. Locals have it down to three words. Ordering “one wiz with” means you’d like one cheesesteak (denoted by “one”) with Cheez Whiz® (denoted by “wiz”), and with fried onions (denoted by “with”). Similarly, saying, “one provolone without,” will secure you a cheesesteak with provolone cheese and no fried onions. Got it?

The art of cheesesteak preparation lies in the balance of flavors, textures, and what is often referred to as the ‘drip’ factor. You’ll know you have a good cheesesteak if juices are dripping from the bun. In order to avoid ruining their clothes, Philadelphians have learned the “Philadelphia Lean.” It’s advised that you do the same. Follow their example by bending forward to eat your cheesesteak instead of bringing it to your mouth.

As you might imagine, there’s much more to Philadelphia and CHEST 2008 than cheesesteak. Learn more about Philly’s cultural, culinary, and recreational options at www.gophila.com, and watch for details about CHEST 2008, October 25-30, at www.chestnet.org.

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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 severe皮肤reactions have been reported in patients receiving beta-lactam antibiotics. These reactions may occur even if prior exposure to the drug was without reaction and may occur even if the patient had a history of sensitivity to a beta-lactam antibiotic. Serious skin reactions, including toxic epidermal necrolysis and anaphylaxis, have been reported in patients receiving beta-lactam antibiotics. Anaphylaxis is a potentially fatal reaction and requires emergency treatment with epinephrine and other emergency measures.

Hypersensitivity 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: Carbamates may reduce serum valproic acid concentrations to subtherapeutic levels, resulting in loss of seizure control. Serum valproic acid concentrations should be monitored periodically 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]

Gastrointestinal Disorders: Severe diarrhea that may be pseudomembranous colitis has been reported in patients receiving β-lactam antibiotics, including DORIBAX™. Pseudomembranous colitis, which may be mild to life-threatening, is characterized by the following: severe watery diarrhea with Blood or mucus in stools and abdominal cramping. If severe diarrhea occurs, DORIBAX™ discontinuation, fluid and electrolyte replacement, and appropriate antibiotic therapy may be necessary. [See Substitution and Dosage Information]

Geriatric Use: Doripenem was safe and well tolerated in 96 elderly patients aged 65-100 years (75 years or older) in the postmarketing setting. Elderly subjects had greater doripenem exposure relative to non-elderly subjects; however, this increase in exposure in some older individuals cannot be ruled out.

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

Nursing Mothers: Doripenem is distributed in breast milk at therapeutic concentrations. Doripenem is not recommended for use in breastfeeding mothers.

DORIBAX™ is a carbapenem antibiotic that is indicated in the treatment of complicated intra-abdominal infections, complicated urinary tract infections, and suspected or proven infections caused by susceptible strains of the designated Gram-negative bacterial pathogens.

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)
- Clostridium difficile-associated diarrhea (see Warnings and Precautions)
- Development of drug-resistant bacteria (see Warnings and Precautions)
- Pneumonitis with inhalational injury (see Warnings and Precautions)

Adverse Reactions from Clinical Trials: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be compared directly to rates in the clinical trials of another drug or to rates in clinical trials of another indication observed in practice. During clinical investigations, 453 adult patients were treated with DORIBAX™ IV (500 mg dosed over 1 hour) in the three comparative phase 3 clinical studies; in some patients, parenteral therapy was followed by a switch to an oral antibacterial. doripenem was superior to comparators in these clinical studies.

The most common adverse reactions 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.

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 III Clinical Trials

<table>
<thead>
<tr>
<th>System organ class</th>
<th>DORIBAX™ 500 mg q8h (n = 477)</th>
<th>Levofoxacin 250 mg IV q24h (n = 472)</th>
<th>DORIBAX™ 500 mg q8h (n = 477)</th>
<th>Meropenem 1 g q8h (n = 469)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>11 14</td>
<td>12 13</td>
<td>12 13</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Phlebitis</td>
<td>4 4</td>
<td>5 6</td>
<td>5 6</td>
</tr>
<tr>
<td>Gastro-intestinal disorders</td>
<td>Nausea</td>
<td>4 6</td>
<td>12 9</td>
<td>12 9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 10</td>
<td>11 11</td>
<td>11 11</td>
<td></td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>Neutropenia</td>
<td>2 1</td>
<td>10 5</td>
<td>10 5</td>
</tr>
</tbody>
</table>

Adverse reactions due to DORIBAX™ 500 mg that occurred at a rate ≥ 1% in other indications 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.

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. Culture and susceptibility information should be 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.

** Includes reactions reported as allergic and bullous dermatitis, erythema, maculopapular eruptions, angioedema, urticaria, pruritis, anaphylaxis and 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.

[10157600B 10/2007]

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</tr>
</thead>
<tbody>
<tr>
<td>Skin and subcutaneous disorders</td>
<td>Anaphylaxis</td>
<td>2 3</td>
<td>1 1</td>
<td>1 1</td>
</tr>
</tbody>
</table>

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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 micro.

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.

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.

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 investigational 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.


For more information, visit us at www.doribax.com