Palliative Care helps hospitals to improve patients’ quality of life and match patients’ goals to treatments, said Dr. R. Sean Morrison.

**Palliative Care Report Card: Hospitals Earn ‘C’**

**BY ALICIA AULT**
Elsevier Global Medical News

Hospitals are rapidly adding palliative care services, but their availability is widely disparate, according to a report that gave a grade of “C” to the state of palliative care services in the nation’s hospitals. Overall, 53% of U.S. hospitals with 50 or more beds reported offering palliative care, according to the report card that was compiled by the Center to Advance Palliative Care (CAPC) and the National Palliative Care Research Center (NPCRC), which is based at Mt. Sinai School of Medicine in New York.

But geographic access varies widely, the report found. In three states—Mississippi, Alabama, and Oklahoma—10%-20% of hospitals offer palliative care. In Vermont, every hospital offers the service. The results were published online in the Journal of Palliative Medicine (2008 Oct. 2 [doi: 10.1089/jpm.2008.0053]).

Hospitals were graded on patient access to palliative care services, patient access to board-certified palliative medicine specialists, medical student access to clinical training in palliative medicine, and physician access to specialty-level training in the field. The report is based on the American Hospital Association’s 2006 Annual Survey Database and a more recent survey that was mailed to hospitals by the CAPC.

The report excluded psychiatric, hospice, and home health care services, and hospitals that offered palliative care only on an outpatient basis. It also did not include data from New York, which the researchers said was outdated.

Those variants showed no association, however, with asthma that developed after age 4 years, reported Dr. Emmanuelle Bouzigon of the Fondation Jean Dausset-Centre d’Etude du Polymorphisme Humain, Paris, and her associates (N. Engl. J. Med. 2008 [doi:10.1056/NEJMoa0806604]).

The findings indicate that early life events play a critical role in the pathogenesis of asthma, and that the early-onset form of the disease is pathobiologically distinct from the late-onset form, the researchers noted. Previously, in a genomewide linkage analysis that was part of the Epidemiological Study on the Genetics and Environment of Asthma, “we showed that markers in the 17q21 region were linked to asthma susceptibility in the presence of environmental tobacco smoke,” they said. They have now analyzed the same data set to further explore those associations.

The researchers genotyped 38 single-nucleotide polymorphisms (SNPs) on chromosome 17q21 in DNA samples from 1,543 patients in 372 families that had probands with asthma. A total of 11 SNPs were significantly associated with the disease. Among those patients with early-onset asthma (by age 4 years), there was a significant association between the SNPs and asthma development. Among 179 families in which all children had exposure to environmental tobacco smoke, the associations between the 11 SNPs and early-onset asthma were similar to those from smoking tobacco. Among 179 families in which all children had exposure to environmental tobacco smoke, the associations between the 11 SNPs and early-onset asthma were similar to those from smoking tobacco.

**See Early Onset** page 4

**AVAIL Trial Negative for Overall Survival**

**BY PATRICE WENDLING**
Elsevier Global Medical News

STOCKHOLM — Bevacizumab in combination with cisplatin and gemcitabine chemotherapy did not significantly improve overall survival in the first-line treatment of nonsquamous non–small cell lung cancer in the final analysis of the phase III AVAIL trial.

With 12.5 months of follow-up, median overall survival reached 13.6 months in patients receiving bevacizumab 7.5 mg/kg (hazard ratio, 0.92; P = .42), 13.4 months in those receiving bevacizumab 15 mg/kg (HR, 1.02; P = .76), and 11.1 months in patients receiving chemotherapy alone, Dr. Christian Manegold reported in a late-breaking abstract at the European Society for Medical Oncology Congress.

The finding is disappointing, as the AVAIL (Avastin in Lung) study was positive for a significant improvement in the primary end point of progression-free survival in both the final analysis and an earlier analysis. Also, a previous trial showed that the addition of bevacizumab to carboplatin and paclitaxel chemotherapy improved overall survival in this setting.

The median progression-free survival in the final analysis was 6.8 months with low-dose bevacizumab (HR, 0.75; P = .0003), 6.6 months with high-dose bevacizumab (HR, 0.81; P = .0456), and 6.2 months with chemotherapy alone.

The data confirm results (6.7 months vs. 6.5 months vs. 6.1 months) reported in 2007 by Dr. Manegold at the annual

**See AVAIL page 2**
Palliative Care Varies

The Midwest had the highest prevalence of hospitals with palliative care programs (65%), followed by the Northeast, and the West. In the South, only 41% of hospitals overall have palliative care. There were some regional differences to the general trends. Montana, a largely rural state, had the second-highest prevalence, with 88% of hospitals offering palliative care. Dr. Morrison said that one of the pioneering palliative care programs in the state was set up in response to how many Montana hospitals have palliative care. The report also pointed out a need for palliative care training to meet the needs of an estimated 90 million Americans living with a serious or life-threatening illness. At least one hospital palliative care program is affiliated with 88% of private U.S. medical schools and 82% of state-founded schools. There are no postgraduate fellowship training programs, however, in 23 states and Washington. The 2,651 physicians who have board certification in palliative medicine translates to 1 certified physician per 31,000 people living with a serious or life-threatening illness. In comparison, there are 16,800 cardiologists (or 1 per 71 patients with myocardial infarctions) and 10,000 oncologists (or 1 per 145 newly diagnosed cancer patients). A new certification program in hospice and palliative medicine being offered by the American Board of Medical Specialties should help the field grow, Dr. Morrison said. But the “dramatic growth in the number of young physicians entering palliative care [is] not quite enough to staff all these programs that are developing, so we also need to see midcareer people make a shift.”

Hospitals overall have palliative care. Dr. Morrison said he was not sure why programs were few and far between at these facilities. Palliative care is offered in 41% of public hospitals and 29% of sole community provider hospitals, creating a disparity of access for many urban, rural, and isolated areas.

NSCLC Trial Data Debated

Among these patients, there was a trend toward improved overall survival with bevacizumab over chemotherapy alone (8.7 months vs. 7.3 months; HR, 0.84). During a discussion of the study, Dr. Jean-Charles Soria, professor of medicine and medical oncology at University Paris XI, and a cancer specialist at Institut de Cancérologie Gustave Roussy in Villejuif, France, noted that second-line therapies could be “polluting” the overall survival advantage in the phase III trials. Dr. Soria emphasized that overall survival was improved about 20% with the addition of bevacizumab to paclitaxel and carboplatin in the Eastern Cooperative Oncology Group 4599 study (N. Engl. J. Med. 2006;355:2542-50). If the survival results from the two studies are pooled, he calculated that there is a significant 11% reduction in the risk of death with the addition of bevacizumab.

There is a clear efficacy signal with bevacizumab, said Dr. Soria; however, he cautioned that it is not the mandatory standard because the extent of benefit of the triplet therapy is within the same range as the best double therapy in this specific population. If bevacizumab is prescribed, patients should be warned about the potential for additional toxicity, and should balance the extent of clinical benefit with the cost and reimbursement issues associated with bevacizumab, Dr. Soria added.

The trial was sponsored by Roche, which markets bevacizumab in Europe. Dr. Manele reported conflicts of interest with Roche, Amgen Inc., Boehringer-Ingelheim GmbH, Eli Lilly & Co., Merck & Co., Novartis, and Sanofi-Aventis. Dr. Soria disclosed conflicts of interest with Roche, Abbott, Eli Lilly, GlaxoSmithKline, Merck-Serono, Pfizer Inc., and Sanofi-Aventis.

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Rehabilitation, and pediatric hospitals. Children’s hospitals were excluded because many pediatric palliative care programs are within general acute care facilities and there was no way to distinguish them, said Dr. R. Sean Morrison, director of the NPCRC. Veterans Affairs hospitals were also excluded because the government requires every VA facility to offer palliative care, said Dr. Morrison, who is a co-author of the report.

Hospitals with more than 100 beds were most likely to have palliative care, with 75% reporting a program. Non-profit hospitals and hospitals affiliated with a medical school were also more likely to offer a palliative program. Only 20% of for-profit hospitals report offering palliative care. Dr. Morrison said he was not sure why programs were few and far between at these facilities. Palliative care is offered in 41% of public hospitals and 29% of sole community provider hospitals, creating a disparity of access for many urban, rural, and isolated areas.

The 2,651 physicians who have board certification in palliative medicine translates to 1 certified physician per 31,000 people living with a serious or life-threatening illness. In comparison, there are 16,800 cardiologists (or 1 per 71 patients with myocardial infarctions) and 10,000 oncologists (or 1 per 145 newly diagnosed cancer patients). A new certification program in hospice and palliative medicine being offered by the American Board of Medical Specialties should help the field grow, Dr. Morrison said. But the “dramatic growth in the number of young physicians entering palliative care [is] not quite enough to staff all these programs that are developing, so we also need to see midcareer people make a shift.”

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*Estimated breaths for a person of 83 years. †Estimated breaths for a person of 81 years. ‡Estimated breaths for a person of average life span.

with every 10 cigarettes young women smoke each day, the risk for ischemic stroke increases significantly, based on results from a retrospective study of more than 1,000 women aged 15-49 years. Many studies have shown that current smoking increases the risk for ischemic stroke, but few studies have focused on young, diverse populations and none have addressed the role of cigarette volume on stroke risk in young women in particular, wrote Dr. Viveca M. Bhat of the University of Maryland, Baltimore, and colleagues.

In this study, the researchers reviewed data from 466 women who had suffered a stroke (cases) and 604 women with no history of stroke (controls) who participated in the Stroke Prevention in Young Women Study, an ongoing population-based study of risk factors for stroke in young women. Of the women who had strokes, 211 were white, 216 were black, and 39 were another race. Of the control women, 331 were white, 229 were black, and 44 were of another race. The study population included 506 women who had never smoked, 184 current smokers, and 184 former smokers. Current smokers were those who had smoked within 30 days of their stroke (cases) or their entry into the study (controls) and who also had smoked more than 100 cigarettes during their lifetimes (Stroke 2008 Aug. 14 [Epub doi: 10.1161/strokeaha.107.510073]). Overall, current smokers were more than 2.5 times as likely to have a stroke as were women who had never smoked, after the researchers controlled for multiple variables including age, race, medical history, and oral contraceptive use.

The risk of stroke was significantly higher for women who smoked as few as 1-10 cigarettes daily, compared with those who never smoked. And the odds of stroke increased significantly as the number of cigarettes smoked per day increased—from more than twice the risk for women who smoked 1-10 cigarettes daily to more than nine times the risk for women who smoked 40 or more cigarettes daily (See box.)

The dose-response relationship was not modified by any of the covariates, including race, the researchers noted. There was no increased stroke risk among former smokers, compared with women who had never smoked. In addition, the risk of stroke for women who smoked, compared with women who had never smoked, increased significantly as the years of smoking increased. But smoking amount, not smoking duration, was the only significant predictor of stroke when both smoking amount and duration were included in the same statistical model.

The study was limited by the possibility of recall bias among the study participants and by the lack of data on alcohol consumption and physical activity, but the use of a large, diverse study group strengthened the results.

The researchers reported no financial conflicts of interest.

Asthma Susceptibility

Early Onset • from page 1

Dr. Gerald H. Koppelman of Groningen (the Netherlands) University Medical Center said in an editorial accompanying the report. "When more is known regarding the mechanisms by which genetic variation at this locus alters susceptibility to asthma, ways to translate these findings into clinical practice may become more apparent," they noted (N. Engl. J. Med. 2008 [doi:10.1056/NEJMgt080756]).

The study findings also support "the notion that asthma is not one disease, but merely the clinical manifestation of several different disease entities," Dr. Holloway and Dr. Koppelman added.

Dr. Nicolas Honanita, FCCP, comments: This is a very interesting study that not only confirms a link between environmental tobacco smoke exposure and asthma in early childhood, but also demonstrates a possible genetic link for the susceptibility to asthma in that group of patients. Of interest is that this genetic link was not found in children who develop asthma later on in life, suggesting a different mechanism for the disease onset. This is yet another confirmation of the gene/environmental interaction that occurs in patients with asthma.
Assay Distinguished Squamous, Nonsquamous NSCLC

BY MITCHEL L. ZOLER
Elsevier Global Medical News

PHILADELPHIA — A new molecular test distinguished between squamous and nonsquamous non-small cell lung cancers with a sensitivity and specificity of 90% or greater, based on results from 73 specimens.

The ability to reliably distinguish squamous from nonsquamous non–small cell lung cancer (NSCLC) is important, because at least two anticancer drugs are indicated for the nonsquamous forms (adenocarcinoma and large-cell lung carcinoma) but are not indicated for squamous NSCLC, explained Dalia Cohen, Ph.D.

Dr. Cohen presented the study findings in a poster session at a conference sponsored by the American Association for Cancer Research.

The labeling for bevacizumab (Avastin) has a warning about an increased risk for hemorrhage when the drug is used in patients with squamous NSCLC. Newly revised labeling for pemetrexed disodium (Alimta) specifies an indication only for the nonsquamous form of NSCLC. About 80% of NSCLC is of the nonsquamous type.

When NSCLC is classified as squamous or nonsquamous by standard methods, pathologists disagree in roughly 30% of cases, said Dr. Cohen, chief scientific officer of Rosetta Genomics in Jersey City, N.J. Rosetta Genomics developed a polymerase chain reaction (PCR) test for categorizing NSCLC as squamous or nonsquamous based on quantifying a particular sequence of microRNA in the specimen.

The microRNA-based assay underwent validation testing in a laboratory at Columbia University Medical Center in New York. Positive results from the study led to approval of the test for clinical use in July by the New York State Department of Health’s Clinical Laboratory Evaluation Program.

The microRNA test should be commercially available through Columbia University later in 2008, according to a press release from Rosetta Genomics. The test is expected to cost about $3,000, according to a Rosetta spokesperson.

MicroRNA are small RNA fragments that do not code for specific proteins but help control gene expression. They are highly tissue specific.

Dr. Cohen and her associates at Rosetta screened the microRNA content of more than 60 squamous and nonsquamous NSCLC specimens. They identified one microRNA species that was 15 times more common in squamous NSCLC specimens than in nonsquamous specimens.

A quantitative PCR test was then developed for that microRNA species and initially tested in 44 NSCLC specimens, both squamous and nonsquamous. Based on those results, high-confidence cut points were established that clearly distinguished between the squamous and nonsquamous specimens.

About 80% of the 44 specimens gave results that fell within the high-confidence ranges. Another cut point was identified that could distinguish between the remaining squamous and nonsquamous specimens, but with a lower level of confidence.

The test was then validated at the Columbia University laboratory using 27 specimens from confirmed squamous cell carcinomas and 32 confirmed nonsquamous cell carcinomas. PCR testing failed in three of the squamous specimens and three of the nonsquamous specimens.

Among the 24 squamous specimens with results that could be evaluated, the PCR test correctly identified 19 with high-confidence results and another 4 with low-confidence results, resulting in a total sensitivity for detecting squamous-cell specimens of 23 out of 24, or 96%, Dr. Cohen reported.

Among 49 evaluable nonsquamous specimens, 43 were identified as nonsquamous with high-confidence results, and another specimen was identified with a low-confidence result. That resulted in a total specificity of 44 out of 49, or 90%.

Overall, 65 (89%) of the 73 evaluable results fell into the high-confidence ranges and 62 (99%) of the 65 high-confidence results accurately identified the NSCLC type.

More specifically, the test correctly identified 19 of 22 specimens that had a high-confidence result for the squamous-cell form, a positive predictive value of 86%.

The test also correctly identified all 43 specimens that had a high-confidence result for the nonsquamous form, a negative predictive value of 100%, Dr. Cohen said in an interview.
Early Acetaminophen Use Linked to Asthma at Age 7

BY DIANA MAHONEY

E xposure to acetaminophen may be an important risk factor for the development of asthma later in childhood, according to new data from an international asthma study. In a sample of more than 200,000 children from 11 countries, those children given acetaminophen—known outside the United States as paracetamol—for fever during their first year of life were about 50% more likely to have experienced asthma symptoms at age 6-7 years than were unexposed children.

Dr. Richard Beasley of the Medical Research Institute of New Zealand, colleagues reported that in phase III of the International Study of Allergies and Childhood (ISAAC), exposure to acetaminophen was significantly associated with increased risk of severe asthma symptoms, as well as rhinoconjunctivitis and eczema at age 6-7 years (Lancet 2008;372:1039-48).

The prevalence of asthma has increased substantially over the past 50 years, as has the use of acetaminophen in children, the authors wrote. Previous studies have reported associations between asthma risk and exposure to acetaminophen in utero, during infancy, and in late childhood and adulthood in populations developed by reduced contact with the phase I of ISAAC identified positive associations between per-person acetaminophen consumption and asthma prevalence in children, they stated.

The current analysis was designed to evaluate the consistency of the association between acetaminophen and asthma and to investigate one of the proposed biologic mechanisms for the link—specifically, that acetaminophen exposure contributes to the development of oxida- nce-induced airway inflammation caused by reduced content of thiol glutathione in the lung and stimulation of the T helper cell 2 response.

Towards this end, parents and guardians of 205,487 children aged 6-7 years from 73 centers were asked to complete two standardized questionnaires. These included a prevalence questionnaire about symptoms of asthma, rhinoconjunctivitis, and eczema, and an environmental questionnaire about possible protective and risk fac- tors for asthma and allergic disorders, including the use of acetaminophen in the first year of life.

The primary outcome measure for the analysis was the association between aceta- minophen use for fever during the first year of life. Of these, 105,015 could be analyzed after data were and included in the multivariate analysis. In this group, the association between asthma symptoms and acetamino- phen use for fever during the first year of life was significant (odds ratio [OR], 1.46). Similarly, the associations between first year aceta- minophen use and rhinoconjunctivitis and eczema were significant (ORs, 1.48 and 1.35, respectively).

Despite the study’s power, size, and multinational nature, the findings do not establish causality because of the study de- sign, the authors stressed. In the absence of an adequately powered, population-based, randomized controlled trial, “evid- ence is insufficient to advise parents and health care providers about the benefits or the risks of taking [acetaminophen] in childhood, or its comparative efficacy and safety with other approaches,” they wrote.

In an accompanying editorial, Dr. R. Graham Barr of Columbia University Medical Center, New York, agreed. “The studies to date are suggestive but not definitive enough to recommend a wholesale change in antipyretic use in children. Acetaminophen has known ben- efits for pediatric febrile illness as well as known toxicities,” he wrote.

The drug might contribute to asthma incidence and it might be prudent to min- imize casual use of this—and all—drugs in the presence of an adequate supply, population-based, randomized controlled trial, “evid- ence is insufficient to advise parents and health care providers about the benefits or the risks of taking [acetaminophen] in childhood, or its comparative efficacy and safety with other approaches,” they wrote.

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Wheezing Illnesses Predicted Later Asthma

BY ELIZABETH MECHCATIE
Elsevier Global Medical News

A history of rhinovirus-induced wheezing illnesses during the first 3 years of life was the most significant predictor that a high-risk child would have asthma at age 6 years, according to a prospective study.

In addition, asthma risk at age 6 was greater in children whose wheezing illnesses were associated with rhinovirus (RV) infections than in children whose wheezing was associated with respiratory syncytial virus (RSV) infection, reported Dr. Daniel Jackson of the departments of pediatrics and medicine at the University of Wisconsin, Madison, and his associates (Am. J. Respir. Crit. Care Med. 2008; 178:667-72).

The investigators followed 259 children at risk of asthma from birth through age 6 years; all children had at least one parent with respiratory allergies and/or a history of physician-diagnosed asthma. The children had a total of 454 wheezing respiratory illnesses in their first 3 years, and a viral cause was identified in 90% of patients. The most common causes were RV, detected in 48% of the specimens, and RSV, detected in 21%. By age 6 years, 28% of the children had been diagnosed with asthma.

Compared with children who had either RSV or RV respiratory illnesses but no wheezing, children who had RV-induced wheezing (regardless of RSV infection) were 10 times as likely to develop asthma by age 6 years, while children with RSV-induced wheezing were 2.6 times as likely to develop asthma at age 6.

At age 6 years, 58% of the children who had wheezing illnesses associated with RV, alone or with other viruses, had asthma, compared with 9% of the children who had not wheezed during the first 3 years. A total of 41% of those who had wheezing associated with respiratory illnesses caused by viruses other than RV developed asthma.

The asthma rate among children who wheezed only when they had an infection caused by RV was 53%, similar to the rate among children who wheezed when they had a respiratory illness caused by RV and other viruses (60%).

“We have clearly demonstrated that RV wheezing illnesses in early childhood confer the greatest risk of asthma at age 6 years,” the authors concluded. “Moreover, the risk of developing asthma after outpatient RV wheezing illnesses during the first 2 years of life is increased only in those children who also wheeze with RV.”

The finding that wheezing associated with specific viruses—particularly with RV—was linked to different rates of asthma risk was a “novel aspect” of the study results, the investigators added.

Infants who wheeze when they have a respiratory viral illness, particularly if they are hospitalized, are known to be at an increased risk of asthma, the researchers noted. The study’s findings “expand this paradigm by focusing on outpatient illnesses, and demonstrate that the etiology and severity of viral respiratory infections significantly predict asthma development in a high-risk cohort,” they explained.

The children were part of the Childhood Origins of Asthma (COAST) study, which recently reported that outpatient RV wheezing illnesses during infancy were the most significant predictor of wheezing through age 3 years.
Tie to Need for Acute Care

By Heidi Splete

Baltimore — Obstructive sleep apnea is associated with significant morbidity among hospital inpatients, based on a review of approximately 60,000 hospitalized patients at a single facility during a 2-year period.

"The goal was to characterize the frequency with which OSA patients needed acute care," said Dr. Lisa Wolfe, FCCP, of the division of pulmonary medicine at Northwestern University, Chicago. Dr. Wolfe presented the results of the study at the annual meeting of the Associated Professional Sleep Societies.

Increased morbidity has been associated with OSA in outpatients, but the impact of OSA on inpatients has not been well studied, Dr. Wolfe said. The Joint Commission has invited the medical community to comment on how to reduce the risk of postoperative complications in patients with OSA, as it evaluates guidelines for patient care, she added.

Dr. Wolfe and her colleagues reviewed data from all hospitalized patients at Northwestern Memorial Hospital in Chicago between September 2003 and May 2007. Acute care management was defined as rapid response team calls, code calls, or unplanned transfers to the intensive care unit. OSA was identified based on medical records.

The overall study population of 1,377 patients with OSA required action from a rapid response team, versus 880 of 59,030 patients without OSA (4.1% vs. 1.4%). Similarly, significantly more patients with OSA required code calls, compared with patients without OSA (2.9% vs. 1.7%). On average, one patient with OSA underwent acute care management every 4.5 days.

Among patients with OSA, significantly more nonsurgical patients required acute care than did surgical patients (7.5% vs. 4.1%), but the reasons for this difference were unclear.

"We know that OSA is a predictor for other health problems," Dr. Wolfe said.

The study was limited by its use of medical records and by a lack of data on continuous positive airway pressure (CPAP) therapy, but the findings support results from previous studies and emphasize the need for enhanced monitoring of hospitalized patients with OSA to reduce their use of acute care resources, she noted.

The topic of OSA as a marker of increased mortality in hospitalized patients attracted national attention in the wake of a study conducted at the Mayo Clinic in Rochester, Minn., in 2001, Dr. Wolfe said. In that study, which included patients who had undergone surgery for hip or knee replacements, patients with OSA were significantly more likely to have complications, compared with control patients who didn’t have OSA. The complications often were serious and contributed to longer hospital stays.

Further studies are needed to explore ways to ensure patient safety and to assess the implications of improved screening strategies for hospitalized OSA patients, Dr. Wolfe added. Dr. Wolfe reported that she had no financial conflicts to disclose.

Obstructive Sleep Apnea Tied to Need for Acute Care

$3 Million Grant Targets ICU Bloodstream Infections

BY MIRIAM E. TUCKER

Elsevier Global Medical News

The Agency for Healthcare Quality and Research has awarded a $3 million 3-year contract aimed at reducing central line–associated bloodstream infections in hospital intensive care units nationwide by implementing a comprehensive intervention, which proved to work at Johns Hopkins University in Baltimore and in the state of Michigan.

The new funding was announced in a telephone press briefing on Oct. 1, the day that Medicare’s new rule of nonpayment for certain hospital-acquired infections— including central line–associated bloodstream infections—went into effect.

“The need to align payment with the quality of care delivered is long overdue, and this policy today is really a large first step toward that goal. … I believe we have to pull as many different levers as we can to solve these problems,” said Dr. Peter J. Pronovost of Johns Hopkins University, when asked to comment on the connection between the Medicare policy and the new AHRQ funding.

The AHRQ grant, which is to be awarded to the Health Research and Educational Trust, an affiliate of the American Hospital Association (AHA), continues the agency’s previous funding for work led by Dr. Pronovost initially at Johns Hopkins and subsequently by his group in collaboration with the Michigan Health and Hospital Association.

The multifaceted intervention included five specific evidence-based procedures (hand washing, full-barrier precautions during catheter insertion, site cleaning with chlorhexidine solution, avoiding the femoral site, and removing unnecessary catheters). Intensive care units also used daily goals sheets to improve communication among clinicians, a comprehensive unit-based safety program, and an intervention to reduce ventilator-associated pneumonia.

Data on infection rates were collected monthly for up to 18 months (N. Engl. J. Med. 2006;355:2725-32 and J. Crit. Care 2008;23:207-211). The 108 participating Michigan hospitals reported on a total of 1,981 ICU-catheter-days. The median rate of catheter-related bloodstream infections per 1,000 catheter-days decreased from 2.7 infections at baseline to 0.0 at 3 months, which was maintained through up to 18 months of follow-up.

The mean number of infections dropped from 7.7 at baseline to 1.4 at 16-18 months. “This is the largest study published, with the most dramatic improvements for any of the quality and safety problems facing our nation’s health care system,” AHRQ director Carolyn M. Clancy said, noting that an estimated 250,000 central line–catheter–associated bloodstream infections occur every year in hospitals in the United States, leading to 30,000-62,000 deaths.

“These dramatic improvements made everyone sit up and say we can do a whole lot better,” Dr. Clancy said.

What makes his study so unique, according to Dr. Pronovost, is its scientific focus on the delivery of health care. “Part of the failure to deliver safe care is a result of the fact that we haven’t viewed in a scientific way how to deliver care. Science is typically limited to finding genes or finding drugs, but that really messy practice of medicine has been relegated to the art, and we dramatically underfund studies of it.”

Now that AHRQ has followed up its initial support with the new grant, “We’re ready to go full steam ahead” in expanding the intervention to the entire country. “The program’s reach, he commented. “Funding will be used to train staffs at ICUs in 10 or more hospitals in 10 states, said Dr. John R. Combes, president and chief operating officer of the Center for Healthcare Governance at the AHA. He is also interim president of the AHA’s trust that is receiving the grant and that will be conducting the trainings in collaboration with teams from Johns Hopkins, Michigan, and state hospital associations.

Ultimately the plan is to expand the intervention to the entire country. "The project has great potential to significantly reduce infections on a national level," Dr. Combes said.

And, Dr. Pronovost said, the intervention should be applicable to inpatient settings other than ICUs, which were chosen for the study mainly because that’s where most central lines are placed and where the most accurate data are collected.

"The strategy was kicks ‘em in the ICU, showed that the rates come down, and then have those teams take this to the operating rooms and emergency department. That’s what happened in Michigan, and that’s what we hope will happen [elsewhere]," he said.

Dr. Pronovost, a professor in Johns Hopkins’s department of critical care medicine, and surgery, won a $100,000 “genius” fellowship award in 2008 from the John D. and Catherine T. MacArthur Foundation for this work.
in his series of patients with previously un-
diagnosed ANCA-associated vasculitis, added Dr. Caporali of the University of 
Pavia (Italy).

It may be important for ICU physicians to include ANCA-associated vasculitis/sys-
temic vasculitis in the differential diag-
osis for patients admitted to the ICU with unexplained severe systemic manifes-
tations, states the rheumatologist said.

Dr. Caporali presented a retrospective investigation of 76 patients with ANCA-
associated vasculitis—46 with Wegener’s 
granulomatosis and 30 with Churg-Strauss 
systemic vasculitis patients—were the most frequent reasons for 
ICU admission, according to Dr. Caporali.

The reasons for ICU admission includ-
ing multiorgan failure, and both died in hospital 
during this hospitalization.

The 28-day mortality rate was 11%, 
inconsistent results and do not establish the efficacy of ALVESCO in patients 
4 to 11 years of age.

Five of the 10 patients diagnosed in the ICU were admitted because of cardiac in-
volvement, 2 for intestinal manifestations of 
active systemic vasculitis, 2 because of 
alevorol hemorrhage, and 1 for laryngeal 
stridor due to Wegener’s granulomatosis.

Patients with Wegener’s granulomato-
sis had classic prodromal symptoms of 
ANCA-associated vasculitis. These symp-
toms included fever, muco-cutaneous 
ulcers, and pulmonary involvement, and 
they were often attributed to viral or 
infected organisms.

It may be important to include vasculitis in 
the diagnosis of patients admitted 
with severe systemic manifestations.

Few studies have been published in the 
medical literature on systemic vasculitis in the 
setting of the intensive care unit, and 
they are not well studied because the diseases are 
so uncommon.

Dr. Caporali noted that last year inten-
sivists at the Mayo Clinic reported on 38 
consecutive patients with necrotizing small-vessel vasculitis admitted to the 
ICU. Nineteen of these patients had Wegen-
er’s granulomatosis, 16 had microscopic poly-
angitis, 2 had CNS vasculitis, and 1 had Churg-Strauss.

In contrast with the Italian experience, 
in only one-third of the Mayo Clinic cases 
was the diagnosis of vasculitis established 
during this hospitalization. The reasons for ICU admission includ-
ed diffuse pulmonary alveolar hemor-
rhage in 14 patients, sepsis in 5, seizures in 
3, and pneumonia in 2. The median ICU 
length of stay was 4 days (Cent 2007:131: 
972-6).

The 28-day mortality rate was 11%, 
with a 1-year mortality of 29%. That was 
a markedly shorter-term mortality than 
predicted by Acute Physiology and 
 Chronic Health Evaluation (APACHE III) scores.

A German audience member reported 
good success using plasmapheresis in 
patients with microscopic polyangiitis 
and pulmonary involvement, and she asked whether Dr. Caporali had a similarly 
favorable experience.

He replied that all patients in his study 
received the classic combination of high-
dose steroids and cyclophosphamide, al-
though plasmapheresis was added with 
good results in two patients in the ICU 
because of combined intestinal and renal 
involvement.

“I think plasmapheresis could also be a 
good option for patients with alveolar hemorrhage,” he added.

Five of the 10 patients diagnosed in the ICU were admitted because of cardiac in-
volvement, 2 for intestinal manifestations of 
active systemic vasculitis, 2 because of 
alevorol hemorrhage, and 1 for laryngeal 
stridor due to Wegener’s granulomatosis.
Preoperative Pazopanib Active in Early-Stage Lung Cancer

BY PATRICE WENDLING
Elevier Global Medical News

STOCKHOLM — Preoperative mono-
therapy with the investigational antiangi-
genic agent pazopanib reduced tumor
volume in 40 of 35 patients with early-
stage non–small cell lung cancer in a phase
II proof-of-concept study.

Tumor volume decreased in some cases
by as much as 86% after a median of 16
days of oral therapy, lead investigator Dr. Nasser
Altorki, FCCP, and his associates reported at
the European Society for Medical On-
tology Congress. In five (14%) patients, tu-
mor volume increased up to 17%, according
to high-resolution 3-D CT imaging.

‘‘That reduction in volume is very, very
impressive,’’ Dr. Altorki, professor of car-
diothoracic surgery, New York–Presbyter-
ian Hospital and Cornell University in
New York, said during a press briefing. ‘‘To
his knowledge, these are the first results
standing of how these agents work in
early-stage operable lung cancer.’’

Prof. José Baselga, president of ESMO,
told reporters that shrinking the tumor
with a nontoxic therapy before surgery
could ‘‘increase the ease of surgery and the
likelihood of cure.’’

However, the press corps observed that
potentially curative surgery was delayed in
the study by a few weeks while research
was conducted on an experimental drug.

Patients with stage I lung cancer—who
made up the bulk of the cohort—typically
undergo surgery without preoperative
treatment. Patients received pazopanib 800
mg once daily for 2-6 weeks, followed by a
7- to 14-day washout period before surgi-
cal resection and biopsy.

Dr. Altorki said that the patients en-
tered the trial with little expectation of
benefit, and that in most cases they par-
took to further researchers’ under-
standing of how these agents work in
early-stage lung cancer.

The antangiogenic monoclonal antibody
bevacizumab has been shown to be effective
in combination with platinum-based
chemotherapy in advanced-stage lung
cancer. Pazopanib has been somewhat
more active in renal cell carcinoma, ovarian
and breast cancer, and sarcoma.

Follow ing the formal presentation of
the data, study discussant Dr. Luis Paz-
Ares asked, ‘‘What is the meaning of this
change in tumor volume in these really
small tumors? Are they as relevant as re-
versal?’’

Using RECIST (Response Evaluation
Criteria in Solid Tumors) criteria, just 3
(8.5%) patients achieved a partial response,
while 31 (88.5%) had stable disease, and 1
(3%) had progressive disease.

Although the tumor volume assessment
has not been validated as a measure of tu-
mor response, the results are still potent-
ially interesting, especially since 8.5% of
patients also had response by standard REC-
CIST criteria after a very short period of
‘‘TUMOR VOLUME DECREASED
IN SOME CASES BY
AS MUCH AS 86% AFTER
A MEDIAN OF 16 DAYS
OF ORAL THERAPY.’’

treatment.

There was no association between tumor
size and patient age.

The most common adverse events were
hypertension (13 patients), diarrhea (13),
fatigue (13), and nausea (12). Grade 3 tox-
icities were reported in five patients, and
one patient experienced a grade 4 nonfa-
tal pulmonary embolism at 18 days post
surgery.

Treatment was discontinued in four pa-
tients who experienced adverse events,
and in one who needed surgery sooner.

There was no association between tumor
response and the development of hyper-
tension, Dr. Altorki said.

The study was conducted at eight sites
in the United States, Spain, and Israel,
and sponsored by GlaxoSmithKline, mak-
er of pazopanib. Dr. Altorki also has re-
ceived research support from Pfizer Inc.
and OSI Pharmaceuticals Inc.
Investigational Drug Boosts Response Rates in NSCLC

Chicago — Adding the investigational compound CP-751871 to chemotherapy significantly increased overall response rates over those to chemotherapy alone among patients with advanced non-small cell lung cancer in a phase II trial.

The overall response rate was 54% in patients given chemotherapy plus CP-751871, compared with 41% in patients treated with chemotherapy alone, Dr. Daniel D. Karp reported at the annual meeting of the American Society of Clinical Oncology.

Patients with squamous histology did particularly well. In that group, the overall response rate was 78%, said Dr. Karp.

At the 2007 ASCO annual meeting, Dr. Karp presented data on 73 patients and reported a 46% response rate for the CP-751871 arm vs. 32% for the chemotherapy-alone arm.

“There is a very strong scientific rationale for looking at the insulin axis in lung cancer,” he explained. “The liver produces IGF-1, and the IGF-1 receptor has 70% homology with the insulin receptor, and controls cell and body size, growth stimulation, and inhibition of apoptosis.”

This year, final data were available on 150 patients, and the results “continue to be encouraging,” Dr. Karp said.

The trial, sponsored by Pfizer Inc., randomized patients with untreated advanced non-small cell lung cancer (NSCLC) in a 2:1 fashion to receive paclitaxel (Taxol, 200 mg/m²) and carboplatin (AUC = 6) plus CP-751871 at either a 10-mg/kg or a 20-mg/kg dose, or to paclitaxel and carboplatin alone, every 3 weeks for up to 6 cycles.

Of 97 patients in the experimental arm, 52 had an objective response, for an overall response rate of 54%, vs. 22 of 53 patients in the chemotherapy-alone group, which had an overall response rate of 41% (P less than 00001).

Response appeared to be dose dependent; patients who received the higher dose of CP-751871 had an overall response rate of 57% vs. 38% for those who received the 10-mg/kg dose.

Similarly, median progression-free survival was 5 months for patients who received 20 mg/kg of CP-751871, compared with 3.6 months for those who received the lower dose (HR 0.80, P = .07).

In patients with squamous cell histology, progression-free survival was 5.6 months with the higher dose, and 4.3 months in the lower-dose group.

In an additional, single-arm extension of the study, 30 patients with squamous cell NSCLC received 20 mg/kg of CP-751871 and chemotherapy. Here, too, the overall response rate was 78%, Dr. Karp explained.

Responses were assessed by the study investigators using RECIST criteria, and independently verified by study monitors.

“Responses were especially rapid and dramatic in three of the patients, whose tumors disappeared completely,” Dr. Karp said.

The most frequent adverse events were grades 3 and 4 neutropenia and hyperglycemia, both of which were higher in the CP-751871 group, and grade 2 fatigue, also higher in patients who received CP-751871.

“I think it’s very intuitively clear that this agent should be associated with some extra hyperglycemia. We know they are getting steroids, and they get Taxol, and we regularly see some elevations of blood sugar. Five patients had sugars over 500, but they were well managed with fluids and the usual diabetic measures. Occasional insulin was required, but this was all quite manageable,” Dr. Karp said.

Three future phase III studies of CP-751871 in non-small cell lung cancer are planned, he said.

In the question and answer period that followed his talk, Dr. Karp expressed enthusiasm about the study results. “We want to be careful and not overstate it, but we think we’re seeing something dramatic with this regimen,” he said.

Dr. Karp disclosed that he has received research funding from Pfizer.

Dr. Davies disclosed relationships with Bristol-Myers Squibb, Eli Lilly & Co., Genentech Inc., Millennium Pharmaceuticals Inc., Sanofi-Aventis, and GlaxoSmithKline.
Guideline Implementation Challenges

This is part 1 of a 2-part series on implementation of guidelines. The focus of part 1 is barriers and challenges to incorporating guideline recommendations into clinical practice. Part 2 will be published next month with a concentration on the future of guideline implementation.

In this era of increasing accountability, physicians and other health-care providers must be able to increase their level of knowledge and implement changes to their patient care practice founded on current evidence-based non-biased recommendations. Evidence-based clinical practice guidelines (EBGs) can be the provider’s best resource. However, studies suggest that substantial underutilization of EBGs results in patients receiving as little as 54% of recommended care.1 Despite the rigorous methodology and vast resources expended to produce high quality EBGs, research has documented both lack of implementation and poor implementation of these recommendations into actual practice.2-4

So, how should the ACCP (1) effectively disseminate guidelines to providers, (2) increase their "knowledge uptake," and (3) ultimately improve the care provided to patients?

Knowledge exists in two forms:
- Lifelong knowledge in books stored on shelves
- Knowledge in the consciousness of people

The second one is essential. This illustrates the difference between dissemination and implementation.

The ACCP disseminates guidelines through several media, including:
- Publication in CHEST
- Postings on the ACCP Web site
- National Guidelines Clearinghouse
- Guidelines International Network
- PDA downloads of the quick reference guides at the annual meeting and on the Web
- Recommendations, slide sets, patient education, and other tools (algorithms, checklists, etc) provided in print and CD-ROMs and sold as "Clinical Resources"

In addition, endorsing organizations are asked to promote the guidelines to their memberships; press releases are sent to medical and lay media; and guidelines are used in educational programs, ACCP-SEEK questions, and other ACCP products. This is only dissemination and does not equate with implementation.

Barriers to implementation are well known and include lack of time, financial disincentives, and deficits of knowledge, skills, and resources. Although the data are not robust, we know that most educational programs and outreach are relatively ineffective.5

Health-care providers around the world have recognized that successful knowledge transfer through the use of clinical practice guidelines requires a comprehensive, multifaceted approach consisting of four core properties: (1) leadership at all levels, (2) supportive culture, (3) development of effective teams, and (4) greater use of information technology (including the Internet).6

Additionally, Grimshaw and other experts with special knowledge in dissemination of clinical practice guidelines argue that a successful multifaceted approach to guideline implementation must include promotion of the EBG by local experts.7-8 Recommendations from the ACCP regarding translation of EBGs into practice stress that "all guidelines are local," and that "guidelines are only successful if they are supported and adopted by physicians in their local practice environment."9

These must be the innovators and early adopters, but more importantly, they must be respected and credible. System change agents, eg, chief medical officers and hospital administrators, must buy in to the concept as they can provide effective incentives. Creative approaches are needed and must be tested for their effectiveness on patient care processes and outcomes. Read next month’s continuation to learn how the ACCP proposes to improve guideline implementation.

References

PCCU Lessons for November

▶ Emergence of Methicillin-Resistant Staphylococcus aureus
By Dr. Andrew La belle; and Dr. Marin Kollef, FCCP

▶ Mediations: Therapeutic and Adverse Effects on Sleep
By Dr. Asher Qureshi, FCCP

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O bstructive sleep apnea (OSA) is a chronic disease that requires long-term treatment. Continuous positive airway pressure (CPAP) is considered the treatment of choice for moderate to severe OSA. The use of nasal CPAP in patients with OSA has been associated with significant improvement in daytime sleepiness and improved quality of sleep, daytime functioning, and control of BP in select patients with hypertension (Kushida et al. Sleep 2006; 29:375).

However, the long-term benefits of CPAP therapy are only seen in patients who are compliant and adhere to its use. The regular use of CPAP for at least 4 h per night and 5 nights per week was considered acceptable compliance in one of the earliest studies (Levine. Am J Respir Crit Care Med 1994; 149:287). The use of CPAP for at least 4 h was considered the threshold value, because it provided a clinically meaningful benefit that was perceived by the patient. However, the percentage of patients who achieved this threshold value was only 46%.

The recently published guidelines from the Centers for Medicare & Medicaid Services regarding the prescription of CPAP for patients with OSA selected a similar threshold of minimal CPAP use for a patient with OSA to continue to have Medicare or Medicaid pay for CPAP therapy after the initial 90-day prescription period (Centers for Medicare & Medicaid Services. Pub. 100-01, Medicare National Coverage Determinations Manual. Chapter 1, Section 240.4).

Does this mean that patients who use CPAP for 6 to 7 h would not derive any additional benefit? A recent multicenter study (Weaver et al. Sleep 2007; 30:711), which looked at 7 centers and 149 subjects, demonstrated a significant linear dose-response relationship between the increased use of CPAP therapy and achieving normal levels of sleepiness and daytime functioning when CPAP was used up to 7 h.

However, subjective sleepiness, as judged by the Epworth sleepiness scale, improved at 4 h, while objective sleepiness, as determined by multiple sleep latency tests and daytime functioning, showed maximal improvement at 6 and 7.5 h of CPAP use, respectively. The percentage of patients who met the threshold of 4 or more hours of nightly CPAP use was 66%. It also was recognized that there are differences between individuals regarding the hours of CPAP use and the variable treatment outcomes that need further study.

Another retrospective study (Campos et al. Chest 2005; 128:624) reported an increased survival rate in the groups of patients who used CPAP for 1 to 6 h and > 6 h, compared with the group that used CPAP for <1 h. This suggests that, in the case of CPAP therapy, less is not more, and more use of CPAP equates to better outcomes.

The use of CPAP begins with patient acceptance. Acceptance of CPAP therapy is linked to factors such as initial patient perception of the CPAP machine and mask, potential benefits of treatment, claustrophobia, and nasal obstruction.

Long-term adherence to CPAP therapy is linked to patient-related and CPAP-related factors. Patient-related factors that improve adherence to CPAP therapy include patient education, perception of disease severity and responses to treatment; behavioral factors, such as willingness to use CPAP and active coping skills; social/family support; and the availability of support staff for long-term follow up. CPAP-related factors include proper fitting of the mask interface, the type of machine, and the use of heated humidity.

Patient education is a key element in improved adherence to CPAP therapy. Patient education should not only focus on enhancing disease-specific knowledge about OSA, with an emphasis on comorbidity and mortality, but also on disease-specific skills that will promote the use of CPAP therapy. Clinical guidelines for the manual titration of CPAP in patients with OSA emphasize adequate CPAP education, hands-on demonstration, careful mask fitting, and acclimatization prior to titration (Kushida et al. J Clin Sleep Med 2008; 4:157).

Common problems associated with CPAP use, such as nasal congestion, dry mouth or throat, and claustrophobia, can be remedied if patients are educated early. For example, inhaled nasal steroids help decrease nasal congestion and, therefore, enhance compliance. Nasal surgery for nasal obstruction unresponsive to medical therapy is a deviated nasal septum can improve acceptance and adherence to CPAP therapy.

It is well recognized that patient perception of severity of symptoms with perceived treatment benefit enhances adherence to CPAP therapy. Additionally, it makes intuitive sense that patient education that emphasizes the potential benefits of CPAP therapy on improved BP and glucose control (Tasali et al. Chest 2008; 133:496), with the potential for reduction in mortality, also can further enhance the acceptance and adherence to the therapy.

An educated patient is an empowered patient who is more motivated and willing to improve his or her health, with resultant improved acceptance and adherence to CPAP therapy.

CPAP-related measures to improve adherence focus on proper mask fitting, heated humidity, use of the CPAP ramp, and different machine modalities. A proper mask fit is an essential element in patient comfort, the avoidance of an air leak, and compliance with CPAP therapy. There is a wide variety of CPAP masks that range from nasal to full-face masks and nasal pillows, with a variety of headgear to support the stability of the masks through the night. There is no one mask that works best for all patients. The best mask is the one that works best for an individual patient.

The use of the CPAP ramp, bilevel CPAP therapy, pressure relief or flexible CPAP and auto-CPPAP have not been associated with improved compliance in randomized studies but may benefit an individual patient (Kushida et al. Sleep 2006; 29:375).

Adherence to CPAP therapy can be enhanced with added heated humidification. One study (Masse et al. Chest 1999; 116:403) demonstrated that CPAP use was 5.52 h per night compared with 4.93 h per night without humidity. Another randomized study (Mador et al. Chest 2005; 128:2151), however, failed to show improved adherence to CPAP therapy with heated humidification for all patients compared with an approach using humidification for select patients with side effects.

Despite the evidence in the literature, it is the authors’ experience that >50% of the patients using CPAP require heated humidification with resultant improvement in adherence.

The availability of a staff member, either a nurse or a respiratory therapist, who is knowledgeable about sleep apnea and the use of CPAP therapy, is invaluable in providing ongoing support to improve compliance. The support staff should address problems promptly as they arise and, therefore, avoid long delays that reinforce negative perceptions about the lack of benefit and problems with CPAP. The support staff also facilitates communication between patients and the physicians, improving compliance and adherence rates.

The staff support is critical in the first week or first few weeks, because both frequency and duration of CPAP use in the first month reliably predict its use in the third month, with greater potential for long term success (McArdle et al. Am J Respir Crit Care Med 1999; 159:1108).

In one study (Hoy et al. Am J Respir Crit Care Med 1999; 159:1096), the use of nurse-led intensive education and support, which involved several days of titration and home visits, improved the nightly use of CPAP to 5.4 h compared with 3.9 h in the control group. Additionally, a population-based CPAP therapy program that included consistent follow-up, troubleshooting, and regular feedback for patients and physicians helped achieve adherence rates of 84% over 6 months (Sin et al. Chest 2002; 121:430).

More recently, group cognitive behavioral therapy interventions that used a videotape plus standard treatment demonstrated improved acceptance and adherence to CPAP therapy by 2.9 h at 28 days over standard treatment alone (Richards et al. Sleep 2007; 30:635). Alternatively, telemedicine has not been shown to improve adherence to CPAP therapy compared with traditional care (Taylor et al. Sleep Breath 2006; 10:132). This suggests that ongoing support with long-term follow-up that employs multidisciplinary principles of patient education and behavioral treatment intervention can improve adherence to CPAP.

In summary, OSA is a chronic condition that needs long-term treatment. CPAP is an effective therapy for OSA. The challenge is to promote long-term adherence to CPAP therapy that is essential to achieve improved clinical outcomes.

Strategies that are known to enhance CPAP adherence include patient education, patient perception of severity of symptoms and treatment benefit, appropriate mask interface, use of heated humidity, behavior modification with intensive support, and close follow-up.
Does Regular Marijuana Smoking Lead to Pulmonary Disease? Part 1: Marijuana Smoking and COPD

It is reasonable to hypothesize that the smoking of marijuana may have adverse pulmonary consequences.

Marijuana is the second most commonly smoked substance in our society, after tobacco. According to the latest survey of marijuana use in the United States,1 among young adults (19 to 30 years of age), the prevalence of marijuana use is 27% with in the past year and 16% within the past month (considered current use), while 5.0% of young adults report smoking marijuana on a daily basis.

Corresponding prevalence figures for tobacco use in the same age group are 36% for use within the past year, 27% for current use, and 19% for daily use.

The pulmonary consequences of tobacco smoking are well known and include COPD and bronchogenic carcinoma, which together account for nearly 300,000 deaths in the United States each year.2,3 Since the predominant mode of marijuana use is by smoking and since the smoke contents of marijuana include many of the same respiratory irritants and pro-carcinogens that are found in tobacco smoke,4-6 it is reasonable to hypothesize that the smoking of marijuana, particularly on a regular basis, may have adverse pulmonary consequences that are at least qualitatively similar to those attributable to tobacco.

In the first of this two part series, I will review the evidence both for and against the hypothesis that marijuana smoking is a risk factor for COPD. In Part 2, I will discuss the relationship between marijuana smoking and the development of lung cancer.

Is Marijuana Smoking a Risk Factor for COPD?

Chronic Respiratory Symptoms

The association of marijuana smoking with chronic respiratory symptoms was systematically assessed in three published studies,2-4 two of which examined consecutive samples of young to middle-aged adults residing in Los Angeles, CA (average age 32 to 37 years) or Wellington, New Zealand7 (average age 41 to 46 years), and the other a randomized stratified sample of the residents (aged 15 to 40 years) of Tucson, AZ.8 All three studies controlled for the confounding effect of concomitant tobacco use.

The Los Angeles study showed a significantly higher prevalence of symptoms of chronic bronchitis (chronic cough and sputum) and wheezing, as well as wheeze, and a higher incidence of acute bronchitis episodes in those who smoked marijuana only (MS) compared with control nonsmokers (NS).

No significant differences in symptom prevalence or incidence of acute bronchitis were noted between the marijuana-only (MS) and tobacco-only (TS) smokers, and no additive effect of marijuana and tobacco on symptoms in the dual smokers of both substances (MTS) was apparent.

In the Tucson study, cough, phlegm, and wheeze were also more common in the MS than the NS (significantly so for sputum and wheeze), but cough and sputum were less prevalent than among TS, and additive effects of marijuana and tobacco on respiratory symptoms were observed in the MTS.

In the Wellington study, symptoms of chronic bronchitis were equally prevalent among MS and TS, compared to a significantly lower prevalence in NS, and twice as prevalent among MTS compared with single-substance smokers.

All three studies showed an association between marijuana smoking and chronic bronchitis, independent of the effect of tobacco, although the studies differed somewhat in regard to the comparative effects of marijuana vs tobacco and the additivity of the effects of marijuana plus tobacco on respiratory symptoms.

The latter differences were probably due to differences in the characteristics of the study samples, particularly with regard to age and marijuana smoking history.

The smokers of marijuana alone in the Los Angeles and Wellington cohorts consisted of only heavy, habitual users (mean joint-years of smoking (number of joints/day X years smoked) 56.7 and 54.2 years, respectively), while the MS in the Tucson cohort had smoked significantly less marijuana (mean 8.1 years).

In support of the possibility of additive effects of marijuana and tobacco, the Vancouver BOLD study,9 a survey of a random community-based sample of 878 people 40 years of age for evidence of COPD showed a substantially higher odds ratio for chronic respiratory symptoms of chronic bronchitis, wheezing, and dyspnea for MTS vs NS (OR 17; 95% CI, 1.2-2.9) than for TS vs NS (OR 1.8; 95% CI, 1.2-2.6).

Interestingly, none of the other above cited studies reported an increased prevalence of dyspnea in association with marijuana smoking.

Lung Biopsy Studies

Bronchoscopic studies conducted in a subgroup of the Los Angeles cohort provide insight into the bronchial pathologic condition underlying the increased prevalence of symptoms of chronic bronchitis among the marijuana smokers.

Light microscopy of bronchial mucosal biopsy samples in 40 MS, 31 TS, 44 MTS, and 53 NS revealed extensive histopathologic alterations in the epithelium of MS, including goblet cell hyperplasia, reserve cell hyperplasia, and squamous metaplasia. The proportion of MS exhibiting these specific histologic abnormalities (68%, 73%, and 83%, respectively) was significantly higher (p<0.05) than that of NS (29, 12, and 6%, respectively) and comparable to that of TS.10

The results are also consistent with findings in rats involving exposure to increasing concentrations of marijuana or tobacco smoke over 1 year that led to the morphologic and physiologic changes in the lungs of animals exposed to a similar quantity of marijuana.11 Conversely, two other studies involving the cohort from Tucson and a birth cohort from Dunedin, New Zealand examined lung function, cross-sectionally and/or longitudinally, in well-characterized cohorts of MS, TS, MTS, and NS.6,12-14

In the Los Angeles cohort, all spirometric indices, including the forced expiratory flow rate between 25% and 75% of the forced vital capacity (FEF 25-75%), a sensitive measure of small airways function, and the single-breath diffusing capacity for carbon monoxide (DLco), a sensitive but nonspecific physiologic indicator of emphysema, were within normal limits in MS and not different from the results in NS.9 In addition, among MS, the annual rate of change in FEV1, measured over 8 years, was not significantly different from that of NS.12

In contrast, TS exhibited significant decrements compared with control NS in FEF25-75% as well as a significantly greater annual rate of decline in FEV1 than NS.12

These findings suggest that heavy habitual smoking of marijuana, in the absence of tobacco, does not produce the early or progressive physiologic changes that precede the clinical development of COPD.

These results are consistent with findings in rats involving exposure to increasing concentrations of marijuana or tobacco smoke over 1 year that led to the morphologic and physiologic changes of emphysema (decreased alveolar surface area and reduced lung elastic recoil) only in the tobacco-exposed rats but not in the animals exposed to a similar quantity of marijuana.11

More importantly, in both of these cohorts, the airflow obstruction progressed over time in the continuing marijuana users.12-14

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

Editor’s Insight

Dr. Tashkin raises an important concern about the relationship between marijuana smoking and the development of chronic lung disease. It is an important point for me to remember as a clinician. Although I routinely ask about cigarette smoking and illicit drug use, I rarely specifically ask about the actual intensity of marijuana smoking. In my clinical practice, I will have to be diligent about exploring this issue with my patients.

continued on following page
In contrast to the Los Angeles study, these two reports suggest that regular use of marijuana may be a risk factor for the subsequent development of COPD.

Possible support for these conclusions is provided by the Vancouver BOLD study, which reported an OR for the development of spirometrically confirmed COPD of 3.6 (95% CI: 1.5-9.0) for MTS vs NS, compared with 2.2 (95% CI: 1.2-3.9) for TS vs NS.

On the other hand, the Wellington study failed to find a significant detrimental effect of marijuana (in contrast to tobacco) on FEV1, FEV1/FVC, or FEF25-75%.

**Conclusion**

Regular marijuana smoking is associated with symptoms of acute and chronic bronchitis and evidence of microscopic injury to bronchial lining cells.

However, evidence is inconsistent as to whether habitual marijuana use is associated with mild airflow obstruction or with an accelerated decline in lung function that is likely to lead to COPD.

Further research is required to resolve these conflicting findings, especially when we recognize the widespread use of marijuana.

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To encourage and inform ACCP members and Ambassadors Group members who want to help The CHEST Foundation further its efforts in tobacco prevention education, a new DVD, “Lung Lessons™: A Presenter’s Guide” was created. Filled with helpful information on how to present The CHEST Foundation’s Lung Lessons™ program, this DVD was distributed at the Women’s Health NetWork Luncheon, The CHEST Foundation booth, and the Ambassadors Group Hospitality and Information Room during CHEST 2008. It includes clips from last year’s session at CHEST where Ambassadors Group members, Monir Almassi, Susan Kvale, and Kathy Wilder taught a demonstration lesson in front of 12 elementary school children. The DVD also contains information about where to secure resources to teach the Lung Lessons™ program in your local schools. The CHEST Foundation has created a Lending Library where volunteers can borrow materials, such as the Lou Wheree Smoker’s Lung Kit, Mr. Gross Mouth, and a laminated Lung Anatomy poster to make their presentations more interesting to middle-school students. The DVD will also be made available on The CHEST Foundation’s Web site under the section of Tobacco Prevention at www.chestfoundation.org.

This Month in CHEST—Editor’s Picks

By Dr. Richard S. Irwin, FCCP
Editor in Chief, CHEST

- Circulating Carbon Monoxide Level Is Elevated After Sleep in Patients With Obstructive Sleep Apnea. By Dr. M. Kobayashi, et al.
- The Obesity Paradox in Patients With Peripheral Arterial Disease. By Dr. W. Galal, et al.

Topics in Practice Management
- The Basics of Medical Malpractice: A Primer on Navigating the System. By Mary Ellen Nepps, JD.

G/W Commentary: Medical Malpractice and the Chest Physician. By Dr. J. M. Luce, FCCP.

G/W Editorial: Management or Avoidance of Medical Malpractice Crises? Time To Choose. By Dr. D. M. Studdert.

Contemporary Reviews in Critical Care Medicine
- Critical Management Decisions in Patients With Acute Liver Failure. By Dr. R. T. Stutroz

www.chestjournal.org

Session Rewind

- Hear Sessions You Missed
- Replay Sessions of Value
- Share Sessions With Colleagues

CHEST 2008 sessions will be available for purchase as audio reproductions of the sessions presented. When available, faculty handouts are included, as well. Audio files will be available for most general sessions, postgraduate courses, abstracts, and case reports. Sessions are available individually or by clinical track. Audio files can be downloaded to a memory stick, personal computer, or other electronic device. You can also purchase a pen/flash drive, available in the ACCP store at chestnet.org, on which to download files. Sessions will not be available on CD.

The Science and Practice of Sleep Medicine

SLEEP Medicine 2009

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Doubletree Paradise Valley Resort
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Plan to attend this 4-day review of developments and updates in clinical sleep medicine and take advantage of:
- Relevant, practical instruction to help increase your knowledge of sleep medicine and expand patient care skills
- Expanded clinical workshops, including two dedicated to portable monitoring and technological advances in the delivery of PAP
- Dedicated lectures covering the legal and business aspects of managing and directing a sleep lab or practice
- Increased interactive lecture time, featuring keypad technology and question and answer sessions

Visit us at www.chestnet.org for more details and to register.
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Intensivist
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Pulmonary/Critical Care Opportunity

Gundersen Lutheran Health System is seeking a BC/BE Pulmonary/Critical Care physician. Join a well-established group of six board certified pulmonary and critical care physicians.

Responsibilities will include critical care, inpatient and outpatient pulmonary medicine, sleep medicine, bronchoscopies and other invasive procedures on a rotational basis. All pulmonary physicians actively participate in the teaching program and clinical research.

Join the team that ranks:
• HealthGrades Critical Care Excellence Award
top 5 percent in the nation for Overall Critical Care
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top 5 Star Rated and Highest Possible Star Ratings for Treatment of Sepsis (2 years), Treatment of Respiratory Failure, Treatment of Diabetic Acidosis and coma

Gundersen Lutheran Health System offers an excellent work environment, competitive salary and great benefits package.

Contact Jon Nevala, manager, medical staff recruitment, at (800) 362-9567, ext. 54224, or email jrnevala@gundluth.org Visit online at gundluth.jobs

Northern California
Hospitalist Opportunity

Sutter Medical Group is seeking a Hospitalist to join their successful expanding Hospitalist program in Auburn, CA. Candidate must have two years of recent experience doing procedures and be able to handle ICU coverage.

• 2-year shareholder track
• Generous compensation
• Competitive benefits package
• Excellent retirement package
• Wide variety of shifts available
• School system is one of the best in CA
• Great quality of life

Sutter Auburn Faith Hospital is a medium sized hospital with a 24/7 hospitalist program, open ICU, high resolution CT scan, cardiac cath lab, full nuclear medicine department, bronchoscopy suites and a pulmonary function laboratory.

The community of Auburn is nestled in the Sierra Nevada foothills approximately 35 miles northeast of Sacramento. Auburn is known for its family-oriented atmosphere and for its excellent schools. Residents enjoy year-round outdoor recreations such as golfing, hiking, biking, and white water rafting.

Contact: Rhonda Beamer, Walchi Tauber Group, Inc., 2225 Old Emmorton Road, Suite 201, Bel Air, MD 21015. (443) 512-8899 Ext. 106. FAX: (443) 512-8909.

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To view additional opportunities, visit www.alphaps.org

Gundersen Lutheran Health System offers an excellent work environment, competitive salary and great benefits package. Affordable housing and wonderful communities to raise a family. Submit CV today! Nicole Berte, Alpha Physician Search, 800.504.3411 or nberte@alphamg.org

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Sutter Medical Group (SMG) is seeking a BE/BC Pulmonary Critical Care physician in Auburn, CA. Good call schedule.

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Clinical interventions are the underpinning of the newly revised guidelines.

BY DR. WILLIAM C. BAILEY, FCCP
CHEST Physician Contributing Writer

D r. Edward Winga, FCCP, a pulmonary specialist at Gundersen Lutheran Hospital in La Crosse, Wis., understands full well the power of persistence. He remembers a patient who refused time and again to consider quitting with his help. A few years later, the patient returned and said, “I quit smoking, Doc.” “What changed your mind?” Dr. Winga asked.

“Well, Doc, you kept after me, so I figured you must be serious.” It took a drumbeat of reminders, but that patient from a mid-sized city on the Mississippi River now knows the benefits of being tobacco free.

And Dr. Winga? He has renewed appreciation for the power of repeated interventions with patients who use tobacco. Research shows that even interventions of less than 3 minutes can make a difference.

Clinical interventions are the underpinning of the U.S. Public Health Service Clinical Practice Guideline: Treating Tobacco Use and Dependence. This update was released at a May 2008 gathering at the American Medical Association headquarters in Chicago that featured former U.S. Surgeon General C. Everett Koop, among others.

The American College of Chest Physicians and 57 other clinical and public health organizations endorsed the updated guideline. In an endorsement letter, ACCP President Alvin V. Thomas, Jr., FCCP wrote, “We recognize the quality of the process and the importance of these guidelines.”

Chest physicians and other clinicians who advocate quitting smoking can more than double a patient’s chances of breaking the addiction. Approximately 70% of smokers visit their physicians annually, representing countless opportunities for intervention.

Tobacco-using patients can fall into three groups: Those who are willing to try quitting at this time, those unwilling to make a quit attempt, and former tobacco users. Patients who have never used tobacco or who have been abstinent for an extended period should be congratulated on their status and encouraged to maintain their tobacco-free lifestyle.

For tobacco users, the 5 A’s strategy (ask, advise, assess, assist, and arrange) is invaluable.

Clinicians are urged to ask every patient at every visit about tobacco use. If a patient uses tobacco, they will benefit from being advised to quit in a clear, strong, personalized manner. A clinician can assess someone’s willingness to make a quit attempt. For the patient willing to make a quit attempt, the next step is to assist. Clinicians should consider what medications and/or counseling would move this patient toward success.

Finally, for the patient willing to make a quit attempt, arrange for follow-up beginning with the first week after the quit date.

For patients unwilling to make a quit attempt at the time, address tobacco dependence and willingness to quit at the next clinic visit.

When a patient is willing to quit, the updated guideline stresses that the combination of counseling and medication is significantly more effective than either alone. When at all practical, both should be provided.

The FDA has approved seven medications for tobacco-use treatment. The medications are the nicotine patch, nicotine inhaler, nicotine nasal spray, nicotine lozenge, nicotine gum, bupropion, and varenicline. The guideline recommends all of these medications.

Further, the guideline indicates certain combinations of first-line medications have been shown to be effective treatments as well.

Effective combination medications are long-term use (greater than 14 weeks) of a nicotine patch and other nicotine replacement, such as gum or nasal spray.

The nicotine patch combined with the nicotine inhaler is also recommended, as is the nicotine patch with bupropion SR.

However, medication should not be used when contraindicated—and the guideline does not recommend it for pregnant women, light smokers (defined as less than 10 cigarettes a day), adolescent smokers, or smokeless tobacco users.

The guideline recommends counseling for these individuals, and the evidence supporting the effectiveness of counseling for each of these groups is strengthened.

Some patients may be unwilling to make a quit attempt. Those individuals may lack information about the harmful effects of tobacco use and the benefits of quitting, may lack the required financial resources, may have fears or concerns about quitting, or may be demoralized because of previous relapse.

Such patients may respond to brief motivational interventions that are based on the principles of motivational interviewing (MI), a directive, patient-centered counseling intervention.

There is evidence that MI is effective in increasing future quit attempts among patients who are unwilling to make a quit attempt at this time.

For more, the Guideline Update is available at www.surgeongeneral.gov/tobacco, or by calling 1-800-358-9295.

In addition to the full Guideline Update, a “pocket guide” for clinicians and a brochure for smokers can be accessed through the Web or by calling for copies.

Dr. Bailey is professor of medicine and medical director of the Lung Health Center, University of Alabama at Birmingham.
**WARNINGS AND PRECAUTIONS**

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

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

**Seizure**

Seizure control. Serum valproic acid concentrations should be measured frequently after initiating carbapenem therapy. Alternative anticonvulsant therapy should be considered if serum valproic acid concentrations cannot be maintained in the therapeutic range or seizures occur. (See Drug Interactions)

**Clostridium difficile-Associated Diarrhea:** Clostridium difficile-associated diarrhea (CDAD) has been reported with nearly all antibacterial agents and may range in severity from mild diarrhea to toxic colitis. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of C. difficile.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated. (See Adverse Reactions)

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

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

**Adverse Reactions**

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

- **Anaphylaxis and severe hypersensitivity reactions** (see Warnings and Precautions)
- **Interaction with sodium valproate** (see Warnings and Precautions and Drug Interactions)
- **Clindamycin-associated diarrhea** (see Warnings and Precautions)
- **Development of drug-resistant bacteria** (see Warnings and Precautions)
- **Pneumonitis with inhalational use** (see Warnings and Precautions)

**Adverse Reactions from Clinical Trials:** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of another drug may not reflect rates observed in clinical practice.

During clinical investigations, 853 adult patients were treated with DORIBAX™ IV (900 mg administered over 1 hour q8h) in the three comparative phase 3 clinical studies; in some patients, parenteral therapy was followed by a switch to oral antiamoebic medication. (see Clinical Studies) (14) in full Prescribing Information) The median age of patients in these studies was 54 years (range 18–94) in the pooled comparative cIAI study and 46 years (range 18–94) in the pooled phase 3 clinical trials. The most common adverse reactions (≥ 5%) observed in the DORIBAX™ phase 3 clinical trials were headache, nausea, diarrhea, rash and phlebitis. During clinical trials, adverse drug reactions that led to DORIBAX™ discontinuation were nausea (0.2%), anaphylactic reaction (0.1%) and rash (0.1%).

**Adverse reactions due to DORIBAX™ IV (900 mg q8h) occurred at a rate ≥ 1% in either indication are listed in Table 1.** Hypersensitivity reactions related to intravenous antibiotic use and C. difficile colitis co-occurred at a rate of less than 1% in the three controlled phase 3 clinical trials.

<table>
<thead>
<tr>
<th>Complicated Urinary Tract Infections (one trial)</th>
<th>Complicated Intra-Abdominal Infections (two trials)</th>
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<tbody>
<tr>
<td><strong>System organ class</strong></td>
<td><strong>System organ class</strong></td>
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<tr>
<td><strong>DORIBAX™</strong></td>
<td><strong>Levofoxacin</strong></td>
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<tr>
<td><strong>organ class</strong></td>
<td>500 mg</td>
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<tr>
<td><strong>(n = 226)</strong></td>
<td><strong>(n = 232)</strong></td>
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<tr>
<td><strong>Nervous system disorders</strong></td>
<td>Headache</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td>4</td>
</tr>
<tr>
<td><strong>Gastro-intestinal disorders</strong></td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
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<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td><strong>Anemia</strong></td>
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<tr>
<td><strong>Skin and subcutaneous disorders</strong></td>
<td>Pruritus</td>
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<td>Rash</td>
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<tr>
<td><strong>Infections and infestations</strong></td>
<td>Oral candidiasis</td>
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<td></td>
<td>カンピロバクター性</td>
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</tbody>
</table>

- Includes reactions reported as allergic and bullous dermatitis, erythema, maculopapular eruptions, urticaria and erythema multiforme
- Includes reactions reported as alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, and transaminases increased
- An adverse drug reaction was defined as an undesirable effect, reasonably associated with the use of DORIBAX™ that may occur as part of its pharmacological action or may be unpredictable in its occurrence.

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

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

**Anaphylaxis**

**Neutropenia**

**Drug Interactions**

Valproic Acid: A clinically significant reduction in serum valproic acid concentrations was observed in patients receiving carbenicillin antibiotics and may result in loss of seizure control. Although the mechanism of this interaction is not fully understood, data from in vitro and animal studies suggest that carbenicillin antibiotics may inhibit valproic acid glucuronidase. Serum valproic acid concentrations should be monitored frequently while receiving carbenicillin therapy. Alternative antibacterial or anticonvulsant therapy should be considered if serum valproic acid concentrations cannot be maintained in the therapeutic range or a seizure occurs. (see Warnings and Precautions)

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

USE IN SPECIFIC POPULATIONS

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

**Nursing Mothers:** Doripenem either this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DORIBAX™ is administered to a nursing woman.

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

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

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

Elderly subjects had greater doripenem exposure relative to nonelderly subjects; however, this increase in exposure was mainly attributed to age-related changes in renal function. (see Clinical Pharmacology (12.3)) in full Prescribing Information) In such patients, renal function should be monitored.

**PATIENT COUNSELING INFORMATION**

- Patients should be advised that allergic reactions, including serious allergic reactions, could occur and that serious reactions require immediate treatment. They should report any previous hypersensitivity reactions to DORIBAX™, other carbapenems, other beta-lactams or other allergic reactions.

- Patients should be cautioned that antibacterial drugs including DORIBAX™ should only be used to treat bacterial infections. They should not treat viral infections (e.g., the common cold). When DORIBAX™ is prescribed to treat a bacterial infection, patients should be told that it is common to feel better early in the course of therapy; the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by DORIBAX™ or other antibacterial drugs in the future.

- Keep out of the reach of children.

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BREAK THROUGH

UNLEASH THE POTENCY
BREAK THROUGH

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

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

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

Important Safety Information

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

Serious and occasionally fatal hypersensitivity (anaphylactic) and serious skin reactions have been reported in patients receiving beta-lactam antibiotics. These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens. If an allergic reaction to DORIBAX™ occurs, discontinue the drug.

Serious acute anaphylactic reactions require emergency treatment with epinephrine and other emergency measures, including oxygen, IV fluids, IV antihistamines, corticosteroids, pressor amines and airway management, as clinically indicated. Carbapenems may reduce serum valproic acid concentrations to subtherapeutic levels, resulting in loss of seizure control. Serum valproic acid concentrations cannot be maintained in the therapeutic range or seizures occur. 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

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Carbapenem potency that breaks through today’s gram-negative pathogens†-‡

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

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