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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,

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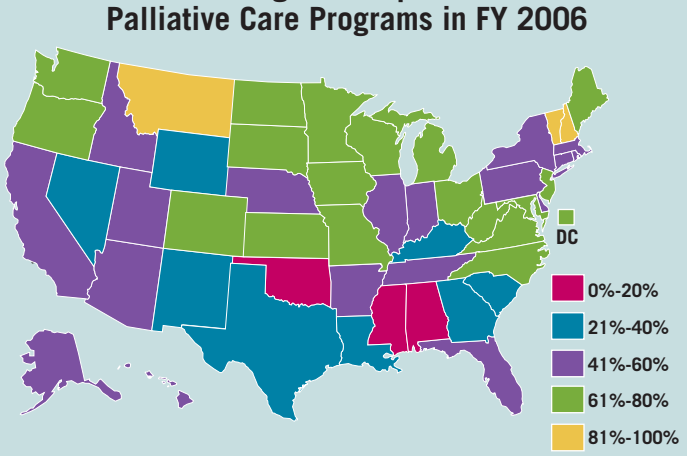
VITAL SIGNS

Percentage of Hospitals With Palliative Care Programs in FY 2006



Sources: Center to Advance Palliative Care and the National Palliative Care Research Center

Elsevier Global Medical News

Early-Onset Asthma Linked to Genes, Secondhand Smoke

But no significant association after age 4.

BY MARY ANN MOON
Elsevier Global Medical News

Gene variants on chromosome 17q21 were significantly associated with the development of asthma by age 4 years, particularly among children exposed to environmental tobacco smoke, according to a report published online in the New England Journal of Medicine.

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

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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 13.1 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, 0.85; $P = .0456$), 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

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INSIDE

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Palliative Care Varies

Report Card • *from page 1*

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, in an interview. Veterans Affairs hospitals also were excluded because the government requires every VA facility to offer palliative care, said Dr. Morrison, who is a coauthor of the report.

Hospitals with more than 300 beds were most likely to have palliative care, with 75% reporting a program. Nonprofit hospitals and hospitals affiliated with a medical school also were 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 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 exceptions 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 was started in the state, which might explain why so 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-funded 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."

Palliative care helps hospitals to improve patients' quality of life and satisfaction, and to match patients' goals to treatments, according to Dr. Morrison. Patients and families are demanding palliative care because it helps them to navigate care for life-threatening illness, he said.

Palliative care offers a coordinated approach to pain and symptom management, and addresses the patient's emotional, financial, and spiritual needs. Palliative care is usually delivered through a multidisciplinary team.

The study was funded by seven nonprofit foundations and the United Hospital Fund, all of which support the CAPC and the NPCRC. The report is online at www.capc.org.

NSCLC Trial Data Debated

AVAIL • *from page 1*

meeting of the American Society of Clinical Oncology. At that time, the overall survival data were not yet mature.

Although the overall survival benefit did not reach statistical significance, Dr. Manegold said the findings should be interpreted in light of two factors: First, the survival time of more than 13 months in all three arms is the longest survival reported so far for advanced non–small cell lung cancer (NSCLC). Second, two-thirds of patients received second-line therapies such as angiogenesis inhibitors, tyrosine kinase inhibitors, and chemotherapy that may have affected outcomes.

"The types of agents used appear to be balanced between the study arms, but unfortunately [we] could not capture specific information on combinations, dosing, and duration of the regimens used, which possibly introduced a bias in the overall survival analysis," said Dr. Manegold, professor of medicine, Heidelberg University Medical Center, Mannheim, Germany.

To control for this confounding factor, an exploratory analysis was conducted among the 272 bevacizumab patients and 123 standard chemotherapy patients, none of whom was receiving second-line therapies. 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 outcome in AVAIL, and that these therapies should be closely evaluated in subsequent 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 doublet chemotherapy 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.

AVAIL enrolled 1,043 patients (median age, 58 years) with previously untreated advanced or recurrent NSCLC and an ECOG performance status of 0-1. Patients received cisplatin 80 mg/m^2 on day 1 and gemcitabine 1,250 mg/m^2 on days 1 and 8 every 3 weeks for up to six cycles, plus either placebo (n = 347), bevacizumab 7.5 mg/kg (n = 345), or bevacizumab 15 mg/kg (n = 351) every 3 weeks until disease progression.

The trial was sponsored by Roche, which markets bevacizumab in Europe. Dr. Manegold 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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CHEST PHYSICIAN

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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.

Note: Calculations are adapted from Brain JD. Control of breathing. The Merck Manual Online Medical Library Web site. http://www.merck.com/mmhe/sec04/ch038/ch038e.html#sec04-ch038-ch038e-17. Accessed August 13, 2008; and Heron MP, Hoyert DL, Xu J, Scott C, Tejada-Vera B; for the Division of Vital Statistics. Deaths: preliminary data for 2006. *Natl Vital Stat Rep*. 2008;56(16):1-52.

Abbott Respiratory

Smoking Tied to Young Women's Stroke Risk

BY HEIDI SPLETE
Elsevier Global Medical News

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 500 women who had never smoked, 386 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.)

LOLITA JONES/ELSEVIER GLOBAL MEDICAL NEWS

Stroke risk rose as the number of cigarettes rose.

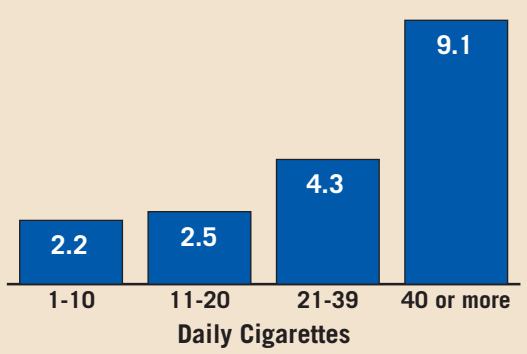
"The dose-response relationship was not modified by any of the covariates, including race," the researchers noted. There was no increased stroke risk among former smokers, compared with women who had never smoked.

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. ■

Odds Ratios for Stroke Risk in Women Smokers, Compared With Women Who Have Never Smoked



Note: Based on data from 1,070 women aged 15-49 years.
Source: Stroke

ELSEVIER GLOBAL MEDICAL NEWS

Too Early to Predict Severity Of Upcoming Flu Season

BY JONATHAN GARDNER
Elsevier Global Medical News

International public health officials responded to reports suggesting that influenza will take a heavy toll this winter by reassuring physicians that it is too early to predict the severity of the influenza season in the Northern Hemisphere.

In separate messages Oct. 2, the World Health Organization and the European Centre for Disease Prevention and Control said the influenza season is just getting underway in the Northern Hemisphere and it is not clear how many people will be affected. There are approximately 500,000 fatalities worldwide each year because of influenza infections.

Several European media reports have suggested that the season will be severe, based in part on the Australian season's unusual severity. However, according to data from the Australian Department of Health and Aging, a total of 6,825 laboratory confirmed cases were reported to the national surveillance system in Australia in 2008 through the end of September, which was 2,913 fewer than occurred over the same period in 2007.

"We simply are not able to say how the season is going to go in the northern hemisphere," Dr. Keiji Fukuda, head of WHO's global influenza program, said in a teleconference to preview the upcoming influenza season. Australian public health officials, "considered this to be a mild season," he added.

Earlier this year, the WHO recommended that all three of the virus strains used in last year's Northern Hemisphere vaccines be replaced with new ones. The new ones are an influenza A/Brisbane/59/2007 (H1N1)–like virus, an A/Brisbane/10/2007 (H3N2)–like virus, and a B/Florida/4/2006–like virus. Dr. Fukuda said, however, that changing the strains in the vaccines was based on their ability to match up with the viruses circulating in the population, not on the expected severity of the season. ■

FDA Approves New Rapid Test To Detect Influenza Viruses

BY LORINDA BULLOCK
Elsevier Global Medical News

The Food and Drug Administration approved a new test that can diagnose human influenza infections, including the highly pathogenic influenza A (H5N1) virus, and produce results within 4 hours.

The device, known as the Human Influenza Virus Real-Time RT-PCR Detection and Characterization Panel (rRT-PCR Flu Panel), was developed by the Centers for Disease Control and Prevention. It is able to detect and identify the most commonly circulating human influenza viruses using a molecular biology technique that can "differentiate between seasonal and novel influenza," according to a written statement released jointly by the FDA and CDC.

The ability to detect those differences facilitates speedier diagnoses, Dr. Frank Torti, FDA principal deputy commissioner and chief scientist, said in the statement. "It will also provide qualified laboratories with a means to rapidly detect new influenza viruses that have not been identified yet and that could pose a pandemic risk."

The FDA and CDC said the device isolates and amplifies viral genetic material present in secretions taken from a patient's nose or throat. That material is analyzed by another device approved simultaneously with the rRT-PCR Flu Panel, called the Applied Biosystems 7500 Fast Dx.

The test will be available to CDC-qualified laboratories as soon as this fall, and some labs will be able to receive free of charge reagents to aid in the testing process.

The CDC, Applied Biosystems Inc., and the Association of Public Health Laboratories collaborated on the development of the new test. ■

Asthma Susceptibility

Early Onset • *from page 1*

were all significant. Among 130 families in which all children were not exposed to environmental tobacco smoke, however, there were no significant associations between the SNPs and early-onset asthma.

There was no significant association between the SNPs and asthma when onset occurred after 4 years of age.

The study "not only increases the understanding of disease pathophysiology, but also can lead to the development of new therapeutic agents," Dr. John W. Holloway of the University of Southhampton (England) and Dr. Gerald H. Koppelman of Groningen (the Netherlands) University Medical Center said in an editorial accompanying the report.

"When more is known regarding the mechanism 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/NEJMe0807576]).

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 Hanania, 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 52 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 (95%) 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
Elsevier Global Medical News

Exposure 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 31 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, Wellington, and his colleagues reported that in phase III of the International Study of Asthma and Allergies in Childhood (ISAAC), exposure to acetaminophen in the first year of life was associated with significantly increased risk of severe asthma symptoms, as well as rhinoconjunctivitis and eczema at 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 from developed and developing countries. Additionally, 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 biological mechanisms for the link—specifically, that acetaminophen exposure contributes to the development of oxidant-induced airway inflammation caused by reduced concentrations of the antioxidant glutathione in the lung and stimulation of the T helper cell 2 response.

Toward 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 factors for asthma and allergic disorders, including the use of acetaminophen in the first year of life and currently.

The primary outcome measure for the analysis was the association between acetaminophen use for fever in the first year of life and asthma symptoms at 6-7 years based on multivariate analysis.

A total of 194,555 children were included in the analysis of acetaminophen use for fever during the first year of life. Of these, 105,041 had complete covariate data and were included in the multivariate analysis. In this group, the association between asthma symptoms and acetaminophen use in the first year of life was significant (odds ratio [OR], 1.46). Similarly, the associations between first year acetaminophen 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 design, the authors stressed. In the absence of an adequately powered, population-based, randomized controlled trial, "evidence is insufficient to advise parents and health care workers of the risk benefit 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 benefits for pediatric febrile illness as well as known toxicities," he wrote.

"The drug might contribute to asthma incidence and it might be prudent to minimize casual use of this—and all—drugs in otherwise healthy children. However, we need to take the guesswork out of recommending and prescribing antipyretic drugs for children."

What is needed, he wrote, are randomized trials that examine the incidence of childhood asthma, comparing acetaminophen use with an active control such as ibuprofen or placebo (Lancet 2008;372:1011-2).

Dr. Beasley reported having received grant support and honoraria for lectures from GlaxoSmithKline Inc., one of the makers of acetaminophen. ■

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 31% 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 RSV 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. ■

DATA WATCH

Top 10 Major Diagnostic Categories for Children
(in thousands of hospital stays)

Note: Based on 2006 data of children 17 years and younger; excludes stays for newborns or perinatal conditions.
Source: Agency for Healthcare Research and Quality

ELSEVIER GLOBAL MEDICAL NEWS

$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;23:207-221).

The 103 participating Michigan hospitals reported on a total of 1,981 ICU-months of data on 375,757 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 program's reach, he commented.

Over the next three years, AHRQ's 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 lick 'em in the ICU, show that the rates come down, and then then have those teams take this to the operating rooms and emergency departments. That's indeed what happened in Michigan, and that's what we hope will happen [elsewhere]," he said.

Dr. Pronovost, a professor in Johns Hopkins's departments of anesthesiology and critical care medicine, and surgery, won a $500,000 "genius" fellowship award in 2008 from the John D. and Catherine T. MacArthur Foundation for this work. ■

Obstructive Sleep Apnea Tied to Need for Acute Care

BY HEIDI SPLETE
Elsevier Global Medical News

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.

"Our 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 2005 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.

Overall, 56 of 1,377 patients with OSA required action from a rapid response team, versus 800 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 surgeries 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 monitoring strategies for hospitalized OSA patients, Dr. Wolfe added. Dr. Wolfe reported that she had no financial conflicts to disclose. ■

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Systemic Vasculitis Often First Diagnosed in ICU

BY BRUCE JANCIN
Elsevier Global Medical News

PARIS — Antineutrophil cytoplasmic antibodies (ANCA)–associated vasculitis is not uncommonly first diagnosed in the intensive care unit, Dr. Roberto Caporali reported at the annual European Congress of Rheumatology.

Cardiac, pulmonary, and intestinal manifestations of systemic necrotizing vasculitis were the most frequent reasons for admission to the intensive care unit (ICU) in his series of patients with previously undiagnosed ANCA-associated vasculitis, added Dr. Caporali of the University of Pavia (Italy).

"It may be important for ICU physicians to include ANCA-associated vasculitis/systemic vasculitis in the differential diagnosis for patients admitted to the ICU with unexplained severe systemic manifestations," 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 syndrome—of whom 12 were admitted to the ICU. In 10 of the 12 patients, the ICU was where the diagnosis of vasculitis was first made.

The two patients whose diagnosis was known prior to ICU admission had advanced disease, and both died in hospital of multiorgan failure.

In contrast, all 10 patients who were diagnosed with vasculitis in the ICU remained alive after a minimum follow-up of 24 months.

Five of the 10 patients diagnosed in the ICU were admitted because of cardiac involvement, 2 for intestinal manifestations of active systemic vasculitis, 2 because of alveolar hemorrhage, and 1 for laryngeal stenosis.

Patients with Wegener's granulomatosis had classic prodromal symptoms of ANCA-associated vasculitis. These symptoms included asthma, sinusitis, nasal polyposis, and/or peripheral eosinophilia for a median period of 3 months prior to their stay in the intensive care unit.

Patients with Churg-Strauss syndrome had prodromal symptoms for a longer period, more than 1 year on average, according to Dr. Caporali.

He said the rheumatic diseases that are most frequently encountered in the ICU are rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, and vasculitis.

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 small in size because the diseases are so uncommon.

Dr. Caporali noted that last year intensivists at the Mayo Clinic reported on 38 consecutive patients with necrotizing small-vessel vasculitis admitted to the ICU.

Nineteen of these patients had Wegener's granulomatosis, 16 had microscopic polyangiitis, 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 included diffuse pulmonary alveolar hemorrhage in 14 patients, sepsis in 5, seizures in 3, and pneumonia in 2. The median ICU length of stay was 4 days (Chest 2007;131:972-6).

The 28-day mortality rate was 11%, with a 1-year mortality of 29%. That was a markedly lower short-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 has had a similarly favorable experience.

He replied that all patients in his study received the classic combination of high-dose steroids and cyclophosphamide, although 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. ■

Preoperative Pazopanib Active in Early-Stage Lung Cancer

BY PATRICE WENDLING
Elsevier Global Medical News

STOCKHOLM — Preoperative monotherapy with the investigational antiangiogenic agent pazopanib reduced tumor volume in 30 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 Oncology Congress. In five (14%) patients, tumor 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 cardiothoracic surgery, New York–Presbyterian Hospital and Cornell University in New York, said during a press briefing. To his knowledge, these are the first results on the effect of angiogenesis inhibitors 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 surgical resection and biopsy.

TUMOR VOLUME DECREASED IN SOME CASES BY AS MUCH AS 86% AFTER A MEDIAN OF 16 DAYS OF ORAL THERAPY.

Dr. Altorki said that the patients entered the trial with little expectation of benefit, and that in most cases they participated to further researchers' understanding of how these agents work in early-stage lung cancer.

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

Following 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 responses?"

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 tumor response, the results are still potentially interesting, especially since 8.5% of patients also had response by standard RECIST criteria after a very short period of treatment," Dr. Altorki said in an interview.

The investigators also analyzed pre- and posttreatment plasma samples for a correlation between 52 cytokine/angiogenic factors and tumor reduction. There was a significant correlation with eight factors: placental growth factor, interleukin (IL)-2 receptor, IL-12, IL-16, tumor necrosis factor–related apoptosis-inducing ligand, stem cell factor, IL-3, and cutaneous T cell–attracting chemokine.

IL-12 was the best predictor of tumor shrinkage, Dr. Altorki said. The combination of placental growth factor and IL-12 may distinguish responding from nonresponding patients.

Dr. Paz-Ares, of the Hospital Universitario Virgen del Rocio in Seville, Spain, also questioned the toxicity associated with using pazopanib in patients with early-stage disease. Of the 35 patients (median age 64 years) in the cohort, 19 had stage IA disease, 14 had stage IB, 1 had stage IIA, and 1 had stage IIB.

The most common adverse events were hypertension (13 patients), diarrhea (13), fatigue (13), and nausea (12). Grade 3 toxicities were reported in five patients, and one patient experienced a grade 4 nonfatal pulmonary embolism at 18 days post treatment.

Treatment was discontinued in four patients who experienced adverse events, and in one who needed surgery sooner. There was no association between tumor response and the development of hypertension, Dr. Altorki said.

The study was conducted at eight sites in the United States, Spain, and Israel, and sponsored by GlaxoSmithKline, maker of pazopanib. Dr. Altorki also has received research support from Pfizer Inc. and OSI Pharmaceuticals Inc. ■

Investigational Drug Boosts Response Rates in NSCLC

BY FRAN LOWRY
Elsevier Global Medical News

CHICAGO — Adding the investigational compound CP-751871 to chemotherapy significantly increased overall responses 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 of the University of Texas M.D. Anderson Cancer Center in Houston.

CP-751871 is a human monoclonal antibody directed against the insulin-like growth factor type 1 receptor (IGF1R) with potential antineoplastic activity. IGF1R is a receptor tyrosine kinase that is expressed on most tumor cells. It is involved in mitogenesis, angiogenesis, and tumor cell survival.

The investigational compound has demonstrated activity as a single agent in Ewing's sarcoma, and in combination with paclitaxel and carboplatin for first-line treatment of non–small cell lung cancer.

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/m^2) 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 six 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 .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., Millenium Pharmaceuticals Inc., Sanofi-Aventis, and GlaxoSmithKline. ■

AMERICAN COLLEGE OF CHEST PHYSICIANS

NEWS FROM THE COLLEGE

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.

SANDRA ZELMAN LEWIS, PHD
Assistant Vice President, Health and Science Policy & Quality Improvement

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 nonbiased 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, 3]

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:

- Lifeless 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, and even audit/feedback and electronic reminders are only moderately effective.[4]

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, [5] 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.[4,7,8] 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. ■

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PCCU Lessons for November

- **Emergence of Methicillin-Resistant *Staphylococcus aureus***
  By Dr. Andrew Labelle; and Dr Marin Kollef, FCCP
- **Medications: Therapeutic and Adverse Effects on Sleep**
  By Dr. Asher Qureshi, FCCP

PCCU
PULMONARY AND CRITICAL CARE UPDATE

NEWS FROM THE COLLEGE

AMERICAN COLLEGE OF CHEST PHYSICIANS

SLEEP STRATEGIES

CPAP Therapy Outcomes: The More, the Better?

Obstructive 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. 100-03, Medicare National Coverage Determinations Manual; Chapter 1, Section 240.4).

Does this mean that patients who use CPAP for 6 to 7 h nightly 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-Rodriguez 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 CPAP compliance. Nasal surgery for nasal obstruction unresponsive to medical therapy or 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-CPAP have not been associated with improved compliance in randomized studies but may benefit an individual patient (Kushida et al. *Sleep* 2006; 29:375).

Sleep Institute® American College of Chest Physicians

Adherence to CPAP therapy can be enhanced with added heated humidification. One study (Massie 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. ■

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Pulmonary Perspectives

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% within 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,[4,5] 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, two of which examined convenience samples of young to middle-aged adults residing in Los Angeles, CA (average age 32 to 37) years)[6] or Wellington, New Zealand[7] (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), as well as wheeze, and a higher incidence of acute bronchitic episodes in those who smoked marijuana only (MS) compared with control nonsmokers (NS).

ALL THREE STUDIES SHOWED AN ASSOCIATION BETWEEN MARIJUANA SMOKING AND CHRONIC BRONCHITIS, INDEPENDENT OF THE EFFECT OF TOBACCO.

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 with 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 8.3 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, 1.2-3.9) 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 33%, respectively) was significantly higher ($p<0.05$) than that of NS (29%, 12%, and 6%, respectively) and comparable to that of TS.[10]

It is highly likely that the increase in the number of mucus-secreting surface epithelial (goblet) cells and the extensive replacement of ciliated epithelium by nonciliated reserve cells and squamous cells resulted in an overproduction of bronchial mucus complicated by an impairment in mucociliary transport in the MS, leading to cough as the fall-back mechanism for clearing the excess sputum from the bronchi and consequent symptoms of chronic bronchitis.

Lung Function Abnormality

While symptoms of chronic bronchitis are often evident in COPD, they are also relatively common in smokers *without* evidence of airflow obstruction, and their absence is common in patients *with* COPD. Consequently, the diagnosis of COPD is based on the demonstration by spirometry of airflow obstruction that is not fully reversible.

Four groups of investigators systematically have examined lung function, cross-sectionally and/or longitudinally, in well-characterized cohorts of MS, TS, MTS, and NS.[6-8,11-14]

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.[6] In addition, among MS, the annual rate of change in FEV_1, measured over 8 years, was not significantly different from that of NS.[12]

In contrast, TS exhibited significant decrements compared with control NS in $FEF_{25-75\%}$, as well as a significantly greater annual rate of decline in FEV_1 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 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 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.[15]

Conversely, two other studies involving the cohort from Tucson and a birth cohort from Dunedin, New Zealand (examined at ages 18, 21, and 26 years), revealed evidence of mild airflow obstruction in association with marijuana use.[8,11]

Moreover, in both of these cohorts, the airflow obstruction progressed over time in the continuing marijuana users.[13,14]

Continued on following page

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 from previous 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,[9] 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 FEV_1, FEV_1/FVC, or $FEF_{25-75\%}$.[7]

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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AMERICAN COLLEGE OF CHEST PHYSICIANS

NEWS FROM THE COLLEGE

Foundation Debuts Educational Product at CHEST 2008

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 Wheeze 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. ■

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

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▶ **The Obesity Paradox in Patients With Peripheral Arterial Disease.** *By Dr. W. Galal, et al.*
▶ **Continuous Aspiration of Subglottic Secretions in the Prevention of Ventilator-Associated Pneumonia in the Postoperative Period of Major Heart Surgery.** *By Dr. E. Bouza, et al.*

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Gundersen Lutheran HEALTH SYSTEM

About Gundersen Lutheran

Gundersen Lutheran is a dynamic top-rated healthcare organization based in scenic La Crosse, Wis. At Gundersen Lutheran, we serve residents of western Wisconsin, southeastern Minnesota and northeastern Iowa. Our healthcare system is anchored by one of the largest multi-specialty group practices and a teaching hospital with Level II Trauma Center. Specialty outreach, telemedicine, distance learning, digital imaging and other services link Gundersen Lutheran with regional clinics, hospital affiliates and practitioners in a 19-county service area.

La Crosse is a historic, vibrant city of more than 50,000 people nestled between bluffs and the legendary Mississippi River. La Crosse boasts a historic downtown and riverfront, a host of festivals and annual celebrations, some of the best outdoor recreation, excellent schools including three universities, affordable housing in safe neighborhoods, an endless variety of live entertainment and breathtaking beauty, making this a great place to call home.

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

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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.
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PHS Updates Tobacco Treatment Guideline

Clinical interventions are the underpinning of the newly revised guidelines.

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

Dr. 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 who have recently quit.

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 medication and/or counseling would move this patient toward success.

Finally, for the patient willing to make a quit attempt, arrange for follow-up beginning within 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.*

INDEX OF ADVERTISERS

DORIBAX™

(doripenem for injection)
for Intravenous Infusion

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

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

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

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated. *[see Adverse Reactions]*

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

Anaphylaxis
Neutropenia

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

Stevens Johnson Syndrome
Toxic epidermal necrolysis
Interstitial pneumonia
Seizure

DRUG INTERACTIONS

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

PATIENT COUNSELING INFORMATION

- Patients should be advised that allergic reactions, including serious allergic reactions, could occur and that serious reactions require immediate treatment. They should report any previous hypersensitivity reactions to DORIBAX™, other carbapenems, beta-lactams or other allergens.
- Patients should be counseled that anti-bacterial drugs including DORIBAX™ should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When DORIBAX™ is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by DORIBAX™ or other antibacterial drugs in the future.
- Keep out of the reach of children.

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

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

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

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

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

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

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

DORIBAX™
doripenem for injection

TOUGH TO RESIST

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

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

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

Important Safety Information

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

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

Carbapenems may reduce serum valproic acid concentrations to subtherapeutic levels, resulting in loss of seizure control. Serum valproic acid concentrations should be monitored frequently after initiating carbapenem therapy. Alternative antibacterial or anticonvulsant therapy should be considered if serum valproic acid concentrations cannot be maintained in the therapeutic range or seizures occur.

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

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

Safety and effectiveness in pediatric patients have not been established.

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

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

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