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CHEST Physician

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Adding cetuximab to platinum-based chemotherapy increased survival by about 1.2 months, said Dr. Robert Pirker.

Cetuximab Combo Tx Boosted NSCLC Survival

BY JANE SALODOF MACNEIL
Elsevier Global Medical News

CHICAGO — Cetuximab improved overall survival of advanced non–small cell lung cancer by about 1.2 months when added to platinum-based chemotherapy in a large international phase III trial that is expected to change first-line treatment for millions of patients.

"Cetuximab added to a platinum-based chemotherapy sets a new standard for the first-line treatment of patients with non–small cell lung cancer," Dr. Robert Pirker, principal investigator of the FLEX trial, announced at a plenary session during the annual meeting of the American Society of Clinical Oncology.

As presented by Dr. Pirker of the Medical University of Vienna, the highly anticipated results for 1,125 patients from 30 countries are mostly positive but also enigmatic.

Median overall survival improved from 10.1 months in 568 patients given cisplatin and vinorelbine by themselves to 11.3 months in 557 patients who had cetuximab (Erbitux) added to their regimen (hazard ratio 0.871, $P = .04$). One-year survival also was better with cetuximab (47% vs. 42%), and the response rate rose from 29.2% to 36.3%.

Progression-free survival stayed flat, however, at 4.8 months for both arms of the study, and a planned subgroup analysis

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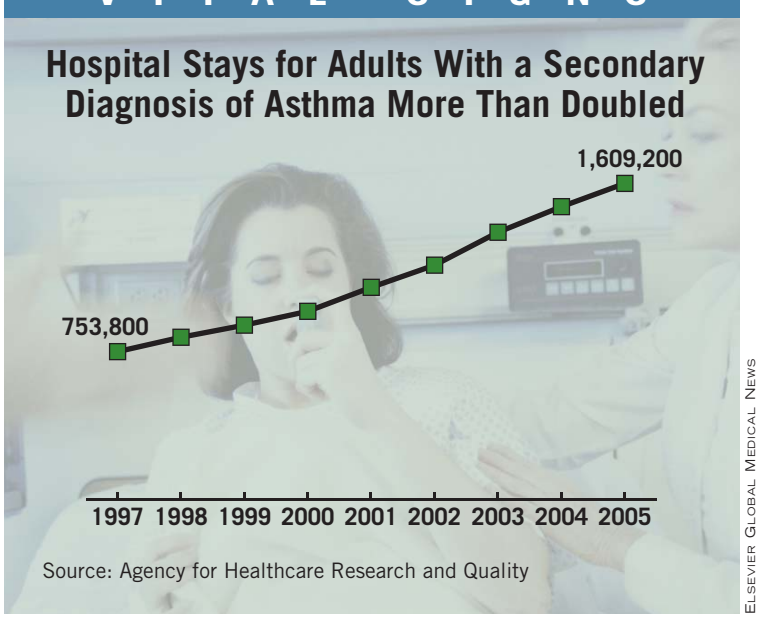
VITAL SIGNS



Elsevier Global Medical News

HHS Reprieve Delays Impact of Medicare Fee Cut

Congress seeks solution to stalemate.

BY MARY ELLEN SCHNEIDER
Elsevier Global Medical News

Although Congress failed to avert a 10.6% Medicare physician pay cut from taking effect July 1, the federal Department of Health and Human Services took short-term steps to minimize the cuts' impact on providers and give lawmakers more time to work out a compromise.

HHS Secretary Mike Leavitt announced at the end of June that the Centers for Medicare and Medicaid Services have instructed the agency's contractors not to process any physician and nonphysician practitioner claims for the first 10 business days of July.

Agency officials estimate that by holding claims for services provided on or after July 1, they will not make payments based on the 10.6% cut until July 15 at the earliest.

With just days to go before the original July 1 deadline, the Senate considered a bill that would have kept the current Medicare payment rates for the rest of 2008 and provided a 1.1% fee increase in 2009. However, the bill was never subjected to an up-or-down vote because a motion to end debate (cloture), which requires 60 votes to pass, failed by 2 votes. The bill, Medicare Improvements for Patients and Providers Act (H.R. 6331), passed the House by an overwhelming margin (355-59) earlier in the week.

Senate leaders will have another chance to pass the legislation when they returned from their week-long recess July 7.

Physician leaders called the lack of action by Congress disappointing and predicted that it could force physicians to limit the number of Medicare patients they care for.

"Failure to pass this legislation does not just impact the physician community," said Dr. Alvin V. Thomas Jr., FCCP,

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INSIDE

Asthma as Secondary Diagnosis Doubles

BY DAMIAN MCNAMARA
Elsevier Global Medical News

Asthma is more often a secondary reason for hospitalization than a principal cause in the United States, and the rate of secondary diagnoses is increasing, according to a report released by the Agency for Healthcare Research and Quality.

The AHRQ's statistical brief "Hospital Stays Related to Asthma for Adults, 2005" indicates that from 1997 to 2005, adult hospital stays specifically for asthma remained stable, whereas the number of secondary asthma diagnoses more than doubled. Asthma hospital stays also varied by socioeconomic status, age, and gender.

Between 2000 and 2005, hospitalizations for asthma increased 18%, from 247,200 to 290,600. However, the number of hospital stays where asthma was secondary rose from 753,800 to 1,609,200, an increase of 113%.

Pneumonia by far led the list of primary diagnoses for hospital stays with a secondary asthma coding in 2005, accounting for 123,100 or nearly 7.6% of these stays, Chaya T. Merril and colleagues at the AHRQ's Healthcare Cost and Utilization Project (HCUP) reported.

Heart failure and nonspecific chest pain were the next most common principal diagnoses, collectively accounting for 121,100 hospital stays or 7.5% with a secondary asthma diagnosis. Osteoarthritis (specifically, degenerative joint disease) and mood disorders (depression and bipolar disorder) were each

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CMS Sees 5.4% Cut in 2009

Medicare Cut • *from page 1*

President of the American College of Chest Physicians. "Included in this Medicare legislative package is a national coverage policy for cardiac and pulmonary rehabilitation, delays in the expansion of competitive bidding for durable medical equipment, and repeals in the mandated title transfer for oxygen equipment—all vitally important issues that impact our ability to care for our patients."

The failed legislation also would have increased bonuses under the Physician Quality Reporting Initiative (PQRI).

Under the bill, the increased physician fees would have been financed in part through cuts to Medicare Advantage plans. Officials at America's Health Insurance Plans, which represents the health insurance industry, estimated that the proposed Medicare Advantage cuts would have resulted in $13.8 billion in budget savings over the next 5 years.

Republican senators who voted against consideration of the bill said sending the legislation to the president would have been useless since he had threatened to veto it if it contained cuts to Medicare Advantage plans. Instead, the senators called for more time to reach a bipartisan compromise.

Sen. John Kyl (R-Ariz.) objected to the legislation, saying that it made "radical changes" in Medicare. The cuts to Medicare Advantage plans would minimize patient choice, he said, and he estimated that about 2 million seniors would have lost their fee-for-service plans by 2013 under the bill.

Physicians have been facing scheduled fee cuts over the last several years, but Congress has usually stepped in at the 11th hour with a temporary fix. Mostly recently, Congress voted at the end of last December to provide a 6-month reprieve on payment cuts and give physicians a 0.5% reimbursement bump.

More Cuts Coming in 2009

For 2009, CMS projected a 5.4% fee cut based on a formula that uses the sustainable growth rate. In 2009, CMS estimates that total Medicare spending under the Physician Fee Schedule will be $54 billion, down from $57 billion in 2008.

The fee-cut estimate was included in the 2009 Medicare Physician Fee Schedule proposed rule. The proposal was published in the Federal Register July 7, and CMS expects to issue a final rule by November.

Aside from projecting a pay cut next year, the Medicare Physician Fee Schedule proposal also offers new measures under PQRI, the voluntary Medicare pay for reporting program. CMS is recommending 56 new measures for 2009, bringing the total number to 175. CMS also is proposing new "measures groups" that allow physicians to report on a subsets of measures related to a certain clinical condition. In addition, CMS plans to begin allowing physicians to report on certain measures through electronic health records in 2009.

The proposed rule also gives physicians a glimpse of the CMS thinking on the possible expansion of the agency's hospital-acquired conditions policy. Beginning Oct. 1, CMS will begin withholding payment to hospitals for certain conditions and infections acquired after admission.

While the agency did not propose any changes in policy, it wrote in the proposed rule that the hospital-acquired condition payment policy could be expanded into other settings, including hospital outpatient departments, skilled nursing facilities, and physician practices. ■

Experts Debate FLEX Data

Cetuximab • *from page 1*

revealed "a remarkable difference" in outcomes of white and Asian patients.

Asian patients lived longer overall, but only white patients seemed to fare better when cetuximab was added to chemotherapy. For 121 Asian patients, median overall survival was 17.6 months with cetuximab and 20.4 months without. The same median was only 9.1 months with chemotherapy alone in 946 white patients, but it rose to 10.5 months with the addition of cetuximab.

Dr. Pirker cautioned against drawing conclusions based on these disparities.

The Asian population was much smaller, he noted, and it had better prognostic factors. "There is no proof that cetuximab does not work in the Asian population. This is not what the FLEX data show," Dr. Pirker said.

The First-Line in Lung Cancer with Erbitux (FLEX) trial was conducted by Merck KGaA in Darmstadt, Germany. It enrolled a broad range of patients who had not been treated for stage IIIB or stage IV non–small cell lung cancer. Nearly half of the patients had adenocarcinoma, about a third had squamous cell carcinoma, and the rest had other subtypes.

All patients in the study received 80 mg/m^2 of cisplatin on day 1 and 25 mg/m^2 of vinorelbine on days 1 and 8 in 3-week cycles. Patients in the cetuximab arm also received an initial dose of 400 mg/m^2 of cetuximab that became 250 mg/m^2 weekly until disease progression or intolerable toxicity.

Skin rash, a common side effect of cetuximab, was the main toxicity and easily managed. Grade 3/4 adverse events were slightly higher in the cetuximab arm: 91% vs. 86% with chemotherapy alone.

The febrile neutropenia rates raised the concern of Dr. Thomas J. Lynch in a discussion at the plenary session. He found the rates high—15% with chemotherapy alone and 22% with the addition of cetuximab—and said the latter rate is unacceptable.

Dr. Lynch, chief of hematology/oncology at Massachusetts General Hospital, Boston, did agree, however, that cetuximab should be an option for first-line treatment in combination with platinum-based chemotherapy.

Having reviewed 15 trials of new agents in NSCLC, he noted that only cetuximab and bevacizumab (Avastin) have been shown to improve overall survival as first-line agents. Cetuximab should be used, he said, for squamous cell histology and maintenance, and for patients who are ineligible for bevacizumab.

He said he was not ready to use it for patients who are eligible for bevacizumab, however, or as a single-agent or a second- or third-line agent. Based on previous phase II studies, he added, cetuximab can be used with other chemotherapy regimens as well.

The Southwest Oncology Group is planning a trial of cetuximab and bevacizumab together against bevacizumab alone, both with paclitaxel-carboplatin chemotherapy.

Cost is an issue. Applying the FLEX data, Dr. Lynch estimated 18 weeks of cetuximab would cost $62,208 at his hospital and $54,000 at a private practice. The cost per year of life gained would range from $540,000 to $622,080.

Use of cetuximab should be restricted to patients whose tumors express cetuximab target EGFR, according to Dr. Lynch. ■

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Celecoxib Assessed in Lung Cancer Prevention Trial

BY MARY ELLEN SCHNEIDER
Elsevier Global Medical News

CHICAGO — Short-term treatment with high-dose celecoxib reduced expression levels for a biomarker associated with precancerous lung lesions in a chemoprevention study of about 200 current and former smokers, according to data presented at the annual meeting of the American Society of Clinical Oncology.

The randomized, double-blind prospective study found a significant reduction in Ki-67 expression, as well as reduced levels of cyclooxygenase-2 (COX-2) in patients who received 400 mg twice daily of celecoxib (Celebrex) for 3 months.

"We cannot sit here and say that taking celecoxib is going to prevent lung cancer. That needs further, larger-scale studies," Dr. Edward S. Kim, the lead author and a medical oncologist at the University of Texas M.D. Anderson Cancer Center, Houston, cautioned at a press briefing at the ASCO annual meeting.

Between November 2001 and September 2006, the researchers enrolled 212 current and former smokers with at least a 20 pack-year smoking history. Most patients did not have a prior cancer, but those who did had been disease free for 6 months. The median age of the study participants was 53 years. The study was funded by a grant from the National Cancer Institute, part of the National Institutes of Health.

Study participants were randomized into four treatment arms: 3 months of placebo, then 3 months of celecoxib; 3 months of celecoxib, then 3 months of placebo; 6 months of celecoxib; or 6 months of placebo. Celecoxib was administered at 200 mg twice daily, and then increased to 400 mg twice daily.

In addition, patients underwent three consecutive bronchoscopies: at study enrollment, at 3 months, and at 6 months. Predetermined biopsies were also performed at the same time.

The study's primary end point was change in the Ki-67 marker (a nuclear protein related to cell proliferation) from baseline to 3 months. Over a 3-month period, high-dose celecoxib, when compared with placebo, did reduce the expression levels of Ki-67 in patients who received 400 mg of celecoxib twice daily. The effect was not seen at the 200-mg dose. The study was designed to detect a 1.2% difference in Ki-67 between celecoxib and placebo with a two-sided 5% level of significance.

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Celecoxib's role in the prevention of lung cancer needs further, larger-scale studies, said Dr. Edward S. Kim.

The researchers also looked at two other biomarkers: COX-2 and NF-kappaB. The COX-2 levels showed a significant decrease with celecoxib treatment at 400 mg, and decreases were close to significant at the 200-mg dose. Levels of NF-kappaB were significantly lowered at the 400-mg dose of celecoxib for former smokers only.

The study does show the safety and tolerability of celecoxib, Dr. Kim said. Three study participants experienced one grade 3 toxicity, but the researchers observed no cardiac toxicities. The study also showed that it was safe for patients to undergo consecutive bronchoscopies, he said.

When the researchers first decided to study celecoxib, prior to the 2001 launch of the study, cardiac safety concerns had yet to be raised about COX-2 inhibitors, Dr. Kim said. In December 2004, officials at the M.D. Anderson Cancer Center voluntarily suspended the trial at the request of the National Cancer Institute and Pfizer Inc., which markets Celebrex.

The study reopened in May 2005 after officials at the Food and Drug Administration recommended that Celebrex continue to be evaluated for cancer treatment and prevention. But before they restarted the trial, the researchers instituted new guidelines, including adding cardiology consultations and evaluations for the study participants.

If researchers choose to study celecoxib, they should try to balance the risks and benefits by identifying patients who are at decreased risk for cardiac events at the outset or focusing on patients with a higher risk for lung cancer, Dr. Kim said. ■

Dr. Philip Marcus, FCCP, comments: *Celecoxib has managed to stay alive despite controversy as to its safety in managing pain and inflammation. The authors have found that its use may actually decrease the risk of lung cancer in susceptible individuals. These findings need to be replicated before it should even be considered for more widespread use in cancer prevention.*

Control of COPD Bolstered by Combo Bronchodilator Therapy

BY NANCY WALSH
Elsevier Global Medical News

TORONTO — Patients with chronic obstructive pulmonary disease treated with a combination of formoterol and tiotropium required less rescue medication than did those treated with tiotropium alone.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has recommended monotherapy with a bronchodilator such as a β_2-adrenergic agonist or an anticholinergic as initial maintenance therapy for patients with symptomatic, moderate to severe chronic obstructive pulmonary disease (COPD). But it has been suggested that combining more than one bronchodilator may confer greater therapeutic benefit, according to Dr. Donald P. Tashkin, FCCP, of the University of California, Los Angeles.

In a 12-week double-blind trial sponsored by Schering-Plough, investigators tested a combination of the long-acting anticholinergic tiotropium plus the long-acting β_2-agonist formoterol to improve symptom control and lessen the need for rescue albuterol to a greater degree than the anticholinergic alone.

The 255 participating patients were aged 40 years or older and had at least a 10 pack-year history of smoking. Postbronchodilator forced expiratory volume in 1 second (FEV_1) was 30%-70% of predicted normal, or 0.75 L, and the ratio of FEV_1 to forced vital capacity was less than 70%.

The researchers performed spirometric measurements weekly, and they recorded in patient diaries the number of puffs of rescue medication. The majority of patients were white men; the average age was 64 years.

Overall daily rescue medication use was reduced by 0.81 puffs/day in the combination group, which was significantly greater than the reduction in the monotherapy group of 0.53 puffs/day, Dr. Tashkin reported in a poster session at an international conference of the American Thoracic Society.

Daytime albuterol puffs were reduced by 1.16/day in the combination group, which also was significantly greater than the reduction of 0.76 in the monotherapy group.

Overall nighttime albuterol use was reduced by 0.44 puffs/day and 0.28 puffs/day in the combination and monotherapy groups, respectively.

Both treatments were generally well tolerated. Four monotherapy patients experienced serious adverse events that were considered to be treatment related, whereas no patients in the combination group experienced serious adverse events.

The rationale for combining an anticholinergic with a β-agonist to improve lung function derives from the drugs' different mechanisms of bronchodilation, Dr. Tashkin wrote in a recent review.

Tiotropium relaxes airway smooth muscle by antagonism of acetylcholine at M3-muscarinic receptors, while formoterol achieves that effect through stimulation of β_2 receptors (Chest 2004;125:249-59). ■

Asthma Rising

Doubles • *from page 1*

noted in 53,000, or 3.3%, of these hospital stays.

Hospitalizations increased with age. Patients aged 65 years and older had more than three times the rate of asthma-related hospitalizations, compared with younger patients. For example, the hospitalization rate per 1,000 population for a primary asthma diagnosis was 0.7 for patients aged 18-44 years, 1.6 for patients aged 45-64, and 2.5 for those aged 65 and older.

Rates also were higher among women—about 2.5 times greater than stays for men. Women had a 1.8 per 1,000 population primary asthma hospitalization rate, compared with 0.7 among men.

Of the 1.9 million asthma-related adult hospital stays in 2005, asthma was a principal diagnosis for 15% and a secondary diagnosis for the other 85%. Mean length of stay was 4.1 days for the primary asthma group and 4.9 days for the secondary group.

Data came from the 2005 Nationwide Inpatient Sample, similar nationally representative samples from 1997 to 2004, and supplemental sources. The database includes all patients regardless of insurance type or uninsured status who were admitted to short-term, nonfederal hospitals. Obstetric and gynecologic facilities; ear, nose, and throat hospitals; and orthopedic, cancer, public, and academic medical hospitals are included.

A total of 74% of the primary asthma inpatient stays were admissions through an emergency department, compared with 51% of the secondary diagnosis stays. In comparison, of the more than 30 million hospital stays in 2005 with no mention of asthma, 48% were emergency department admissions.

Asthma hospitalization rates were higher in poorer areas of the United States, compared with richer regions. For example, adults living in a zip code with a median annual income below $36,000 had a 63% higher rate of asthma-related hospital stays, compared with those residing in a zip code with a higher median income. Medicare and Medicaid were billed for about 60% of asthma-related stays, according to the report.

After accounting for differences in length of stay, hospitalizations principally for asthma cost an average $1,400 per day, or about $400 less than the estimated $1,800 per day for hospital stays with secondary asthma. Aggregate costs were about $1.6 billion for primary asthma admissions in 2005, compared with $14.4 billion for secondary asthma stays.

Researchers found little variation in hospitalizations by region. After adjusting for regional population differences, they found approximately two principal asthma stays per 1,000 population in the Northeast, Midwest, and South. The rate was lower in the West at 1.4 stays per 1,000 population.

Visit www.hcup-us.ahrq.gov/reports/statbriefs/sb54.pdf for a copy of the report. The AHRQ is scheduled to release a second report on pediatric asthma-related hospital stays in August 2008. ■

Noninvasive Ventilation Eases End-of-Life Dyspnea

BY NANCY WALSH
Elsevier Global Medical News

TORONTO — Noninvasive mechanical ventilation alleviated respiratory distress in end-stage cancer patients in a randomized study that compared this palliative modality with the administration of oxygen, Dr. Stefano Nava reported at an international conference of the American Thoracic Society.

"In end-stage cancer we concentrate on relieving bodily pain with morphine but we overlook the pain of the respiratory system, which is dyspnea," said Dr. Nava, chief of the respiratory critical care unit at Istituto Scientifico di Pavia (Italy).

Oxygen is routinely administered along with morphine in this situation, but there has never been a randomized trial evaluating any technique for easing respiratory distress in these patients, and there is no evidence that oxygen is actually beneficial, he said.

To address this uncertainty, the trial was undertaken in six European centers, comparing noninvasive mechanical ventilation (NIV) using a face mask with oxygen administered via nasal cannula.

NIV involves the use of positive pressure to aid in breathing, as does conventional mechanical ventilation, but does not require intubation, Dr. Nava explained.

For enrollment in the study, patients had to have acute respiratory failure and distress, with a Borg dyspnea score greater than 3 and a respiratory rate of more than 25 breaths per minute.

A total of 126 patients were randomized. All of them had solid cancers, and mortality was 80%, as expected, Dr. Nava said. Clearly, survival was not increased. "In fact, we explain to patients that NIV may unduly prolong life, even if only for a few hours," he said.

Overall, there was a similar degree of relief in both groups, but the effects were more rapid with NIV. Borg dyspnea score in the NIV group fell significantly from 6.9 on admission to 5.7 at 1 hour, to 4.7 at 3 hours, and to 3.9 at 24 hours. By comparison, a significant decrease from 6.7 on admission to 5.5 was seen only at 3 hours and to 4.8 at 24 hours in the oxygen group.

Morphine use also was lower in the NIV group in the first 24 hours, at 12.2 mg/day, compared with 19.6 mg/day in the oxygen group.

"This is important for patients, as it allows the sensorium to remain clearer and they are able to say goodbye and sign papers if necessary, which are not trivial things," Dr. Nava commented in a press conference.

With NIV, the mask is worn only intermittently, so the patient also can drink and eat if able.

In Europe, NIV is now used for up to 40%-50% of ventilated patients in the intensive care unit, but it has not yet been widely adopted in North America, he said.

"Easing the struggle for breathing can make a difference to these patients as they are 'knockin' on heaven's door,' in the words of your famous singer, Bob Dylan," said Dr. Nava. ■

Gender Strongly Influences CAP Mortality, Study Reveals

After adjustment for confounders, men were found to be much more likely than women to die within a year.

BY NANCY WALSH
Elsevier Global Medical News

TORONTO — Men who present in emergency departments with community-acquired pneumonia were sicker than women and were more likely to die within the next year, a new prospective study showed.

"We know that gender disparities exist in infection outcomes, with two-thirds of studies in the literature saying that men do worse, and another third suggesting that women do worse," Michael C. Reade, D.Phil., FCCP, said at an international conference of the American Thoracic Society.

"The reason for this is the confounding that occurs whenever you talk about gender influencing anything. Men behave differently than women, and if you are looking for a biological signal, you need to take out all the behavioral, social, and treatment factors that confound," said Dr. Reade of the department of critical care medicine, University of Pittsburgh.

In the largest study to date to investigate sex disparities and treatment outcome, he and his colleagues undertook a prospective observational cohort study between 2001 and 2003 that included 1,136 men and 1,047 women from 28 U.S. hospitals, comparing the effect of gender on illness severity and survival, adjusting for differences in demographic characteristics, chronic health status, health behaviors, and treatment while in the hospital.

Many differences were significant on univariate analysis, although importantly, age was not a factor, he said.

Women were slightly more likely to have insurance and were more likely to have received antibiotics before presenting at the emergency department.

Men had higher Charlson comorbidity scores, with more smoking history and cardiovascular and neoplastic disease. Men also appeared sicker, with mean Acute Physiology, Age, and Chronic Health Evaluation (APACHE III) scores of 37, compared with 39 among women.

Once they arrived at the hospital, men were twice as likely to be sent directly to the intensive care unit and were more likely to receive appropriate antibiotics by 8 hours. Nonetheless, after adjustment for all potential confounders, including race, comorbidities, health insurance, smoking, and prehospital antibiotics, men were much more likely die within the year, with a hazard ratio of 1.3, Dr. Reade said.

Those findings suggest that men presenting with community-acquired pneumonia should be considered a high-risk group, which is not widely recognized, and that the approach currently used probably is not aggressive enough.

"We think this difference must be attributable to biology, because we adjusted for everything else," he said during a press conference. "An interesting question is, Why is this?" Speculation includes potential differences in estrogen levels, Dr. Reade said, or differential expression of inflammation genes on the X chromosome.

Exploring that question will be the next phase of the work, which has been funded by the National Institute of General Medical Sciences. ■

Dr. Mark Metersky, FCCP, comments: *While these results are intriguing, it seems premature to state that the differences "must be attributable to biology," since it is always possible that there are unmeasured confounders in a nonrandomized cohort study.*

D-Dimer and CT May Rule Out Pulmonary Embolism

BY DAMIAN McNAMARA
Elsevier Global Medical News

Inclusion of ultrasonography of the leg did not alter 3-month thromboembolic events in a large group of patients with suspected pulmonary embolism, compared with those assessed with a D-dimer test and multislice CT only, according to a randomized, multicenter study.

"We believe that our findings can be applied to a broad population with suspected pulmonary embolism, and that [the findings] lend support to the hypothesis that a negative MSCT [multislice CT] or ELISA [enzyme-linked immunosorbent assay] D-dimer measurement safely excludes pulmonary embolism in patients with a low or intermediate clinical probability of pulmonary embolism," Dr. Marc Righini, an internist in the division of angiography and hemostasis at Geneva University Hospital, and his associates wrote in the April 19 issue of the Lancet.

They assessed 1,819 consecutive outpatients with a suspected pulmonary embolism (PE) who presented to the emergency department at one of six medical centers in Europe from January 2005 to August 2006. The prevalence of PE was 20.6%. Men made up about 45% of the study population, mean age was 59 years, and about 18% had a personal history of venous thromboembolism.

After exclusions, 855 patients were randomized to double testing with a serum D-dimer assay and MSCT imaging. Another 838 patients had a triple assessment with serum D-dimer, venous compression ultrasonography of the leg, and MSCT.

The primary outcome was the risk of venous thromboembolism events at 3 months in patients who, because of the diagnostic tests' results, were not treated for PE. The thromboembolic risk at follow-up was 0.3% in the double-testing group (2 patients of 673 with complete follow-up) and 0.3% in the triple-testing group (2 patients of 686), thus indicating noninferiority of the double-testing strategy.

"Our results show that ultrasound is no longer required as a safety net for the identification of clots that might have been missed by MSCT," the authors wrote (Lancet 2008;371:1343-52).

The dual-testing strategy was 24% less expensive than the triple-testing protocol, according to a comparison of mean diagnostic test cost per patient. "Therefore, our data do not support the routine use of ultrasound," the authors wrote. "However, ultrasonography might still be an attractive alternative in patients with renal failure or those who have an allergy to contrast dye." They added that ultrasound would only allow avoidance of MSCT in 1 of every 11 patients.

'ULTRASOUND IS NO LONGER REQUIRED AS A SAFETY NET FOR THE IDENTIFICATION OF CLOTS THAT MIGHT HAVE BEEN MISSED' BY MULTISLICE CT.

Possible limitations of the study include a 32% exclusion rate and protocol violations by about 5% of patients, especially those with a high clinical probability of PE and negative MSCT and those with inconclusive test results. In addition, this was a study of outpatients, so applicability of the findings to hospitalized patients is unknown.

In an accompanying commentary, Dr. Paul A. Kyrle and Dr. Sabine Eichinger of the department of medicine at the Medical University of Vienna noted that the researchers are the first to assess this strategy in a randomized trial (Lancet 2008;371:1312-5). "They show that combining clinical assessment, D-dimer testing, and multislice CT is as safe as the approach of D-dimer testing followed by leg ultrasonography and multislice CT. This [current] approach will facilitate the diagnostic work-up of patients with suspected pulmonary embolism and seems to be cost-effective."

The commentators suggested that ventilation-perfusion lung scanning is useful for patients in whom MSCT is contraindicated or results are inconclusive. ■

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A Chronic Care Model for COPD and Its Comorbidities: A Primary Care Initiative

A model now under creation is using principles proven to be effective for other chronic diseases.

COPD is a major cause of morbidity and mortality around the world. Recent evidence suggests that current medical systems are not capable of providing consistent, evidence-based, patient-centered care for chronic illnesses such as COPD. Since most patients receive their COPD treatment from family physicians and internists, improved delivery systems created for the primary care setting could result in greatly improved COPD outcomes. Recently, new models of care have been developed to lessen the burden of chronic diseases, but there has been little attention directed specifically to COPD. To do so is critically important, as the prevalence of COPD continues to increase, especially in women, and it is expected to become the third leading cause of death by the year 2020. Using the GOLD definition of COPD (postbronchodilator $FEV_1/FVC\% < 0.70$ and $FEV_1 < 80\%$ predicted), the NHANES III survey estimated that 23.6 million adults (13.9%) have COPD. An estimated 2.4 million adults, or 1.4% of the population, have severe airways obstruction (GOLD stages III and IV), with an FEV_1 of <50% predicted.

A NATIONAL SURVEY REVEALED THAT COPD PATIENTS RECEIVED 58.0% OF RECOMMENDED CARE OVERALL, JUDGED BY 45 EXPLICIT, PROCESS-BASED QUALITY INDICATORS.

Also concerning are the statistics relating to morbidity and cost of the disease. In 2000, COPD was responsible for 1.5 million ED visits, 726,000 hospitalizations, and 119,000 deaths in the United States. COPD is expected to move up from the 12th leading cause of disability-adjusted life-years in 1990 to the 5th leading cause in 2020, worldwide.

COPD is associated with significant comorbid illness. Patients with COPD are more likely to be hospitalized with pneumonia, hypertension, congestive heart failure, ischemic heart disease, pulmonary vascular disease, thoracic malignancies, and respiratory failure, when compared with age-adjusted patients without COPD. Patients with COPD also have higher age-adjusted in-hospital mortality for pneumonia, hypertension, heart failure, respiratory failure, and thoracic malignancies. Comorbidities are commonly encountered in the outpatient office setting. When primary care patients with newly diagnosed COPD are compared with a control population, the incidences of myocardial infarction and angina are nearly double, and as many as one in five patients will have had previously unrecognized congestive heart failure. The incidence of metabolic syndrome is more than double, and depression and anxiety are four to five times more prevalent. Skeletal muscle wasting, cachexia, anemia of chronic disease, esophagitis, gastritis, and gastric ulcer are other common medical complications, and, overall, COPD is associated with increased odds of osteoporosis compared with patients without airflow obstruction (odds ratio [OR] 1.9; 95% CI 1.4 to 2.5). Patients with severe airflow obstruction are especially at increased risk (OR 2.4; 95% CI 1.3 to 4.4), but moderate disease is also associated with osteoporosis.

During 2000, COPD was responsible for 8 million physician office and hospital outpatient visits. The 2005 National Ambulatory Medical Care survey showed that 4.9% of all ambulatory visits were for COPD, and 52% of all visits were for one or more chronic conditions, such as COPD. One hundred million people in the United States have at least one chronic condition, and half of these individuals have two or more chronic illnesses. Seventy-eight percent of all Medicare beneficiaries reports one or more chronic conditions, and 25% suffers from four or more chronic illnesses. Chronic disease accounts for three-quarters of the total national health-care cost.

In 2004, The National Center for Health Statistics reported that nearly 50% of all ambulatory patient visits were with primary care doctors in office-based practices, 18% were seen in medical specialty offices, and the remaining patients were seen in EDs and by surgical specialists. Unfortunately, in the primary care setting, chronic diseases, such as COPD, are often poorly controlled, despite the existence of established guidelines. The extent to which patients with obstructive lung disease receive recommended care has recently been studied (Mularski et al. *Chest* 2006; 130:1844). In a survey regarding the quality of care delivered to a national sample of the US population, it was discovered that, overall, COPD patients received 58.0% of recommended care, judged by 45 explicit, process-based quality indicators. Care for exacerbations of COPD (60.4%) was somewhat improved over routine care (46.1%).

Barriers to the delivery of optimal care for chronic conditions, such as COPD, have been extensively studied, and the causes, as expected, are due to many factors. The rapid growth of science and technology and complexity of treatment options have been suggested as barriers to the translation of knowledge into practice. The growing complexity of COPD care and recent recognition that it is associated with so many comorbidities will likely compound the deficiencies related in recent surveys.

PATIENTS WHO RECEIVE INTERVENTION WITH TWO OR MORE CHRONIC CARE MODEL COMPONENTS HAVE LOWER RATES OF HOSPITALIZATIONS, POOLED DATA SUGGEST.

Equally important is the inability of our health-care delivery systems to keep up with information technology and multidisciplinary approaches to care and to provide advice regarding principles of self-management. And not inconsequential is the pressure on primary care physicians who are expected to deliver complex care to an aging population with its multiple comorbidities. It has been estimated that in a typical primary care practice, the conscientious physician, who is following established clinical guidelines for the most common chronic conditions, including COPD, will spend 42% of available clinical time on these diseases when the condition is stable. This requires 3.5 hours a day from a primary care physician. But, when the disease is uncontrolled, the estimated time required increases by a factor of three; time demands increase to an unrealistic 10.6 hours a day, leaving no time for urgent care and disease prevention (Ostbye et al. *Ann Fam Med* 2005; 3:209).

To improve the delivery of care to patients with chronic diseases, a sweeping redesign of the health-care system is needed, according to a 2001 report "Crossing the Quality Chasm: A New Health System for the 21st Century" from the Institute of Medicine. Safe, efficient, and effective patient-centered care should be offered by all health-care providers with timely access for all patients, regardless of socioeconomics or ethnicity.

To meet these demands, Dr. Ed Wagner of the MacColl Institute, developed a model of chronic care to guide improvements in primary care of chronic conditions. He and his colleagues have reviewed the use of this model with diabetes, depression, cardiovascular disease, and asthma (Bodenheimer et al. *JAMA* 2002; 288:1775).

The model identifies the following six essential elements for improved care: (1) decision support: the use of evidence-based guidelines for clinical care and availability of specialty support when needed; (2) self-management support: helping patients and their families to take more control of the illness; (3) delivery system design: alter the structure of the medical practice into a team approach with non-physician personnel, for greater efficiency and improved patient access; (4) community resources and policies: providers need to become linked to patient education classes and home care agencies that offer patient services; (5) health-care organization: provider organizations and insurers must have a commitment to the model and a shared vision for improved care; and (6) clinical information systems: a disease registry must be developed to track individual patient needs and testing results and trends in overall care and disease management.

Can the chronic care model improve care for COPD? This question was addressed in a systematic review published in 2007 (Adams et al. *Arch Intern Med* 2007; 167:551). Unfortunately, limited data exist regarding the chronic care model and COPD. There are no studies that have employed all of the elements of the model, but pooled data involving COPD suggest that patients who had received interventions with two or more chronic care model components had lower rates of hospitalizations, lower lengths of stay, and fewer emergency or unscheduled visits.

A comprehensive chronic care model for COPD is needed to reduce the burden of disease and the tremendous cost to patients, their families, and society. The Airway Diseases NetWork of the ACCP has recently joined with the Institute for Healthcare Improvement (IHI), Cambridge, MA, to create a model for COPD and its comorbidities using the principles that have proven effective in other chronic diseases. ■

Dr. Sidney S. Braman, FCCP
The CHEST Foundation and GlaxoSmithKline Second Distinguished Scholar in Respiratory Health

Division Director
Pulmonary and Critical Care Medicine
Warren Albert Medical School
Brown University
Providence, RI

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

Most Adolescents Misjudge Their Asthma Control

BY ROBERT FINN
Elsevier Global Medical News

HONOLULU — Nearly three-quarters of adolescents with asthma overestimate their level of asthma control, according to a study of over 200 teens.

Their degree of overestimation is often large as well, said Dr. Maria Britto of Cincinnati Children's Hospital Medical Center.

Of the 201 adolescents in the study, 54 (27%) judged their asthma to be well controlled when, according to their own symptom reports, it was actually very poorly controlled.

Given this pattern of results, clinicians "should strongly consider using structured questions … to elicit multi-component control, rather than asking global questions such as, 'How's your asthma doing?' " Dr. Britto said at the annual meeting of the Pediatric Academic Societies.

The subjects of the study came from a convenience sample of preteens and teens aged 12 years and older who were seen during routine visits at an urban teen health clinic.

All of these adolescents had previously been diagnosed with asthma, with 58% being judged by their providers as having intermittent asthma, 23% as having mild persistent asthma, 18% as having moderate persistent asthma, and 2% as having severe persistent asthma. (Percentages don't add up to 100 because of rounding.)

The youths averaged 16 years old; 81% were black or African American, 72% had public insurance, and 57% of their mothers had a high school diploma or less education.

Dr. Britto and her colleagues asked the patients specific questions about asthma symptoms and global questions about overall asthma severity. They also asked patients to rate their confidence (on a scale of 1 to 10) in their ability to manage asthma.

Then the investigators used the patients' self-reported symptoms, along with scales developed by the National Heart Lung and Blood Institute, to classify their asthma as well controlled, not well controlled, or very poorly controlled.

On this scale, only 8% of the patients were actually well controlled, although 63% of them believed they were well controlled. Conversely, 46% of the patients were very poorly controlled, although only 3% of them believed they belonged in that category.

Despite this level of inaccuracy in self-assessments, on the whole the patients were quite confident in their asthma management abilities, judging these to be, on average, 7.6 on the 10-point scale.

In a multivariate analysis that controlled for demographic characteristics, asthma severity, and other factors, only two parameters turned out to be significantly associated with overestimation of control: race and confidence.

Compared with white patients, those who were black or African American were seven times as likely to overestimate their asthma control.

And for every 1-point increase on the confidence scale, there was a 19% increase in the likelihood of overestimation. The more confident the patients were, the more likely they were to overestimate their level of control.

Among the patients with poor asthma control, activity limitations and day symptoms were the most frequent contributors to that lack of control (in 79% and 78% of the patients, respectively). Rescue inhaler use was a contributor in 34% of the poorly controlled patients, and night symptoms in 30%.

In responding to a question from the audience, Dr. Britto said that other studies have concluded that adults as well as adolescents often overestimate their level of asthma control. "I think it's not just an adolescent developmental invulnerability perception," she said.

And she expressed surprise at the substantial racial difference in overestimation. "We hadn't expected that there was going to be this huge difference," Dr. Britto said. "We actually hypothesized that age and severity were going to be predictors." She said that the investigators did not have a good hypothesis explaining why race was such a large factor and why age and severity were not.

Dr. Britto had no conflicts of interest related to her presentation. ■

Dr. LeRoy Graham, FCCP, comments: *Identification of poor symptom recognition and thereby poor perception of control is a clear risk factor for the increased utilization and poor asthma outcomes observed in African American adolescents.*

AMERICAN COLLEGE OF CHEST PHYSICIANS

NEWS FROM THE COLLEGE

Philly Delivers Fine Dining, Art During CHEST 2008

Although recognized as the birthplace of the US Constitution, Philadelphia offers much more than cobblestone streets and historical landmarks. CHEST 2008 attendees can expect to find an array of culinary delights, art escapes, and eccentric treasures to satisfy every interest in this vibrant city.

Dining

Philadelphia continues to emerge as one of the country's finest culinary destinations, where four-star dining rooms coexist with unassuming local bistros, foodie hideaways, and family owned establishments. Ethnic restaurants abound.

Looking to sample locally-grown items? You're in luck. Just steps away from the convention center is Reading Terminal Market – the nation's oldest continuously operating farmers' market. Established in 1892, Reading Terminal Market is home to more than 80 unique merchants and sit-down eateries. Here, you can enjoy eating virtually every type of cuisine.

Art and Culture

The Philadelphia Museum of Art's vast collection, ranging from Asian through Renaissance and modern art, makes it a world-class institution and a must-see on any visit. The museum also showcases the famous "Rocky" steps, made popular by the movie.

For the more eccentric eye, check out the Mütter Museum that houses over 20,000 medical-related objects, including fluid-preserved anatomic and pathologic specimens, medical instruments, items of memorabilia of famous scientists and physicians, and medical illustrations.

A local favorite, Franklin Square, is one of the five public squares that William Penn laid out in his original plan for the city.

The park boasts several all-new, family-friendly attractions, including a miniature golf course, a classic carousel, storytelling benches, and the park centerpiece—the Franklin Square Fountain.

Shopping

With a wonderful mix of urban shopping districts, some of the nation's largest retail centers, and tax-free shopping on clothing and shoes, you may find yourself spending more than a few "Ben Franklins" in these trendy retail neighborhoods. One of the most popular shopping districts is the upscale and chic Rittenhouse Row, brimming with art galleries, haute couture boutiques, national stores, specialty shops, luxurious spas and salons, and restaurants and cafés. Located on the Northwest edge of the city, Germantown Avenue is a charming nineteenth century neighborhood offering more than 200 specialty shops and restaurants, along with trendy salons and other modern amenities.

For more information about Philadelphia, visit www.gophila.com. Visit www.chestnet.org for more information about CHEST 2008. ■

CHEST 2008

DATES TO KNOW

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

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

Guest Tours
October 9: Preregistration closes

Philadelphia
October 25-30, 2008

In Touch With CHEST Foundation Awardees

Measuring the value of The CHEST Foundation's awards program in the words of previous award recipients …

Humanitarian Recognition Award

Maria Guevara, MD, FCCP, was one of the recipients of the $5,000 Humanitarian Recognition Award in 2006 for her project, "Médecins Sans Frontières (MSF)/Doctors Without Borders." Dr. Guevara has been involved with MSF since 2004 and has volunteered her time and shared her medical skills in communities located in Liberia, Monrovia, Guatemala, Haiti, Goma, and the Democratic Republic of the Congo. During her award year, she volunteered at medical clinics and a maternity ward in a hospital in Liberia. She reports that thousands of patients have benefited from the volunteer work of MSF physicians. The award funds that the organization received on her behalf covered medications, testing/lab materials, educational materials, and food to meet the needs of the undernourished, impoverished, medically underserved, and insufficiently informed people living in remote areas of Liberia.

Dr. Guevera writes, "The benefit of receiving such an award is certainly the monetary contributions, but also the ACCP recognition of MSF, a nongovernmental organization. The increase in awareness by the College of this organization helps inform many more doctors about our efforts."

THE CHEST FOUNDATION

Clinical Research Award in Women's Health

Varsha Taskar, MD, FCCP, University of Texas Health Center, Tyler, TX, was the 2006 award recipient of the Clinical Research Award in Women's Health. Dr. Taskar's project was titled, "Is There a Relationship Between Anxiety, Depression, Peripheral Vascular Disease, and Hormonal Imbalance Among Women With COPD?" The objective of her cross-sectional study was to examine the relationship between anxiety, depression, hormone levels, and peripheral vascular disease among postmenopausal women with COPD.

The preliminary results of her research thus far suggest that, among postmenopausal women with COPD, there are differences in hormonal levels and psychologic distress associated with the severity of airflow obstruction. She presented her results at the Women's Health NetWork Open Meeting during CHEST 2007. She writes, "I hope that the results will be submitted as an abstract to the 2008 American Thoracic Society International Conference in Toronto, ON, Canada. After completion of the project, the results will be submitted for peer-reviewed publication."

She continues, "The CHEST Foundation funding of this research has given me the opportunity to develop new expertise and prepared me as an independent clinical investigator. The results from this project have resulted in new research questions." ■

NEWS FROM THE COLLEGE

AMERICAN COLLEGE OF CHEST PHYSICIANS®

Innovative Competition Tackles Asthma Epidemic

BY MARILYN A. LEDERER
Executive Director, The CHEST Foundation

Citizens in Chicago may breathe easier, thanks to the business insights of Northwestern University graduate students enrolled in the Kellogg Graduate School of Management. A team of Kellogg School and Feinberg School of Medicine students took first place in the inaugural CHEST Foundation Case Competition, the final round of which was held May 8, 2008, at the James L. Allen Center in Evanston, Illinois. The event was held in collaboration with the Larry and Carol Levy Social Entrepreneurship Lab at Kellogg, as well as the Kellogg Social Impact Club, the Health Industry Management Program, and Healthcare and Biotechnology Club. The goal of the competition was to find a sustainable business solution to address the rising epidemic of asthma among children and families living in underserved Chicago neighborhoods. The competition was organized by Dean Jain from the Kellogg School, CHEST Foundation President-Elect and Kellogg alumnus, John C. Alexander, Jr., MD, FCCP, and former CHEST Foundation Trustee and Kellogg alumnus, Allen I. Goldberg, MD, Master FCCP.

The competition challenged five student teams from Kellogg, Feinberg, and the University of Chicago to devise entrepreneurial solutions that would alleviate asthma, including those undiagnosed. The teams were vying for a first prize of $2,000 and a runner-up prize of $1,000, as well as networking opportunities with a distinguished panel of judges representing industry, nonprofit organizations, and physicians. Among the judges were Dr. Alexander, Dr. Goldberg, David Dravonve and Tim Feddersen from the Kellogg School of Management, and Dr. C. Everett Koop, FCCP(Hon), former United States Surgeon General.

ACCP

(L-R) Al Lever, FCCP(Hon); Dr. Alvin V. Thomas, Jr., FCCP; Dr. C. Everett Koop, FCCP(Hon); Dr. John C. Alexander, Jr., FCCP; and Dr. Allen I. Goldberg, Master FCCP.

Two teams from the original five teams were selected to present their cases to the judges. They were *Home Clean Home* and *Open Mic. Health.*

The *Home Clean Home* team impressed judges with a business plan designed to attack key asthma triggers in the home.

Through an effort to educate people about these triggers, and also help them reduce exposure in the home, the team developed a hybrid for-profit and non-profit business model.

The for-profit arm would raise revenue through a residential cleaning service that specialized in eliminating indoor asthma triggers, while the not-for-profit organization would use these funds to drive a community-based "train the trainers" asthma education program.

The students' polished presentation and attention to financial details earned them top marks and the $2,000 prize.

Runner-up Open Mic. Health earned $1,000 for its proposal to develop a DVD-driven media tool designed to engage and educate patients about asthma. The device, which featured YouTube-like videos created by community members, would be placed in clinics to reach the target audience.

Dean said the collaboration between Kellogg and The CHEST Foundation illustrates the impact that business frameworks can have in the health-care arena.

"This competition is an excellent example of how business schools can play a key part helping practitioners address urgent problems," said Jain. "The solutions our students create and implement can offer profound benefits to the larger community."

Dr. Goldberg commented that "As a Kellogg alum, I know the potential of 'Kellogg power.' This is why I made the challenge to Kellogg students, faculty and alumni to partner with the CHEST Foundation's Communication in Health Care Project, an initiative meant to provide trustworthy, understandable information to disadvantaged populations so they can manage their health, navigate the health system, and find resources they need to do so."

Representatives from *Home Clean Home* and *Open Mic. Health* will be presenting to the annual participants of the asthma coalition symposium at CHEST 2008 in Philadelphia, PA. ■

From the 2008 ACCP Capitol Hill Caucus

Dr. Kalpalatha K. Guntupalli, FCCP, ACCP President-Designate, with Representative Michael Burgess (R-26th, TX).

Dr. Joyce N. Gonzales, Augusta, GA, with Representative Phil Gingrey (R-11th, GA).


ACCP

(L-R) Dr. Vera A. De Palo, FCCP, Chair of the ACCP US and Canada Council of Governors and ACCP Governor for Rhode Island; Dr. William M. Corrao, FCCP; ACCP Past President, Dr. Sidney S. Braman, FCCP; and Senator Sheldon Whitehouse (D-RI).

For a full story on the 2008 ACCP Caucus, see the President's Report in the May 2008 issue of *CHEST Physician*.

ACCP Past President Dr. Susan Pingleton, Master FCCP, Joins UHC

The University HealthSystem Consortium (UHC) has announced that Dr. Susan Pingleton, Master FCCP, has accepted the position of Chief Learning Officer starting July 1, 2008. Dr. Pingleton is a Past President of the ACCP; the former Chair of Internal Medicine and Chief Medical Officer at the University of Kansas; and a recent Petersdorf Scholar at the Association of American Medical Colleges, where she spent the last year studying what residents know about patient safety and how they learn it.

DR. SUSAN PINGLETON, MASTER FCCP

Dr. Pingleton worked with UHC in the past on a number of projects, including the development of the Medical Leadership Council and toolkits for medical directors. She will lead UHC's efforts around member education, particularly in the areas of medical leadership and administration, quality and safety, and performance improvement.

UHC, formed in 1984, is an alliance of 101 academic medical centers and 178 affiliated hospitals, representing about 90% of the nation's nonprofit academic medical centers. ■

AMERICAN COLLEGE OF CHEST PHYSICIANS

NEWS FROM THE COLLEGE

SLEEP STRATEGIES

Portable Monitoring for OSA Diagnosis: Tracking Progress

On March 13, 2008, following years of controversy and debate, the Centers for Medicare & Medicaid Services (CMS) released a groundbreaking announcement regarding diagnosis and management of obstructive sleep apnea (OSA). Many in the field believe this ruling will likely change how sleep and pulmonary specialists care for patients with OSA. A document known as a National Coverage Determination (NCD) proposed that coverage for continuous positive airway pressure (CPAP) would be allowed based on a diagnosis of OSA using portable diagnostic equipment. The determination allows for a 12-week period of coverage for CPAP when OSA is diagnosed by the combination of clinical evaluation and an unattended home sleep apnea test (HSAT). The new proposed rules will allow a variety of home portable testing devices to be used in conjunction with clinical evaluation in making a diagnosis of OSA: type 2, 3, and 4 devices, in addition to a type 1 traditional facility-based polysomnogram. The determination provides reimbursement for CPAP therapy for 12 weeks, and, after that time period, it is based on documented benefit from CPAP therapy.

Sleep Institute® American College of Chest Physicians

So, how did we get here? The controversy between advocates of facility-based technician-attended sleep studies and home-based portable unattended sleep studies has been building for years. The field of sleep medicine developed rapidly in the 1980s based on sleep disorders centers utilizing a standardized, facility-based polysomnogram (type 1) attended by a technologist. Sleep disorders centers also studied other sleep disorders besides OSA, such as narcolepsy, parasomnias, periodic leg movement disorder, idiopathic hypersomnolence, insomnia, and abnormalities of circadian rhythm.

In an attempt to simplify testing for sleep apnea, several commercially made devices have been manufactured over the years, designed to allow the patient to sleep in their own home while being tested. In 1994, the American Sleep Disorders Association (now the American Academy of Sleep Medicine) convened a task force to review the literature on portable sleep monitoring and concluded that evidence in the literature did not support the use of these portable devices in the diagnosis of sleep apnea.

In the following year, CMS (then HCFA) determined it would not reimburse for portable sleep apnea studies. In 1997, the Agency for Healthcare Quality and Research (AHQR) reviewed the literature and reached a similar conclusion. A similar review and finding occurred in 2001. In 2003, the major societies concerned with sleep and pulmonary medicine, the American College of Chest Physicians (ACCP), American Thoracic Society (ATS), and American Academy of Sleep Medicine (AASM), combined resources to produce a comprehensive review of the literature and concluded, again, that there was not sufficient evidence that portable monitoring was equivalent to facility-based type 1 studies in diagnosing sleep apnea. Based on this latter review of the evidence, CMS again concluded that portable studies would not be reimbursed and that CPAP reimbursement would only be based on a facility-based study. In spite of the CMS ruling, managed care organizations across the country, such as Kaiser Permanente,

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continued to utilize portable monitoring devices to diagnose and treat patients with sleep apnea while avoiding the costs of building sleep laboratory facilities.

In March 2007, Dr. David R Nielsen, the Executive Vice President and Chief Executive Officer of the Academy of Otolaryngology and Head and Neck Surgery (AAO-HNS) wrote a letter to CMS requesting a revision of the national coverage determination to allow portable sleep studies. CMS initiated a review of its previous NCD. Public comment from national societies was solicited. ACCP responded with a position paper in April 2007, based on input from the ACCP Sleep NetWork and Sleep Institute, and approved by the ACCP Board of Regents.

CMS then convened a public forum of a Medical Coverage Advisory Commission (MedCAC) at the CMS headquarters on September 12, 2007. The MedCAC consisted of a panel of physicians from specialties other than sleep or pulmonary medicine to review the evidence and hear comments. An independent review of the medical literature conducted by AHRQ was a major focus of the hearing. The ACCP was represented at the hearing by Dr. Charles Atwood, FCCP, and Dr. Richard Castriotta, FCCP. Representatives from ATS, AASM, NAMDRC, AAO-HNS, and industry also attended and provided comments. The MedCAC panel concluded its analysis by answering a series of questions about level of confidence in various ways of establishing a diagnosis of OSA. The final NCD was released in March 2008. At this time, regulations, in conjunction with this decision, are being written by local medical directors for the implementation of the NCD.

It became apparent that the MedCAC changed the focus of the debate in this decision. Previous analysis had focused on the question of which test correlates the best with a "gold standard" test, namely full PSG. The current determination appears to focus on a different question: how best to identify patients with a clinical suspicion of OSA who will benefit from CPAP? This is an outcomes-based approach more than a test of diagnostic accuracy. A major underlying assumption to the decision was that a trial of CPAP is not harmful and has minimal risk. Obviously, this assumption would not be valid if the treatment was a surgical procedure. Therefore, this analysis and NCD by CMS applies only to treatment with CPAP and not to decisions regarding surgical therapy. The shift in viewpoint puts a greater emphasis on the treatment of OSA as a chronic condition and de-emphasizes, to some degree, the focus on diagnosis. This shift in thinking reflects the perspective of members of the ACCP Sleep Institute.

How will this impact ACCP members who care for patients with OSA? While no one knows for certain how the field will be affected, we know for sure that there will be a greater use of home sleep apnea testing in the future. While HSAT will provide greater access to patients, it should also be mentioned that home sleep testing is complicated by a certain percentage of nondiagnostic or artifact-altered studies. Many believe that home sleep apnea testing may raise overall costs or reduce overall quality if the studies are performed by individuals without adequate training and experience and, if appropriate, follow-up is not done. As some observers see it, many patients with a very high clinical probability of OSA and no comorbidities can be identified with home studies. However, for patients who have other significant medical problems, such as COPD, PSG will likely be the best option. Patients with central sleep apnea or Cheyne-Stokes respirations will be best evaluated in the sleep lab. PSGs will also be necessary for other sleep disorders, such as evaluation of hypersomnolence or parasomnias. Many patients will prefer home studies, while many patients will prefer facility-based studies. The result may be that sleep labs will study more complicated and difficult patients, while home portable studies will be used to identify patients with a high probability OSA. Since only a minority of patients with sleep apnea has been diagnosed thus far, the net result may be that sleep specialists will be busier and more in demand. There will also be an emphasis on providing follow-up care. It is certain that ACCP members will be at the front lines in the evolving practice of sleep medicine. The Sleep Institute and the Sleep NetWork will be important stakeholders and sources of up-to-date information. ■

Dr. James Parish, FCCP
Director, Sleep Disorders Center
Mayo Clinic Scottsdale

AMERICAN COLLEGE OF CHEST PHYSICIANS®

NEWS FROM THE COLLEGE

Exploring Einstein and 'The Wizard of Menlo Park'

The Wizard of Menlo Park: How Thomas Alva Edison Invented the Modern World, by Randall Stross. Crown Books, 2007
Einstein: His Life and Universe, by Walter Isaacson. Simon & Schuster, 2007

Prologue

This issue of *CHEST Physician* begins the trial of an occasional feature for our bibliophilic readership. These book reviews will uniquely pair volumes having some connection. These pairings are a casual reflection of this reviewer's intentioned serendipity and not a scholarly effort to pair books of equal authorship and importance. These pairings are meant to enhance the joy of reading, in sequence, books having some link. The books reviewed will, at times, include just-published works, and, at other times, those published many years ago. Despite the date of publication, each book will be available through one or more booksellers or similar Web sites. After all, it is not the reviews themselves but your own enjoyment of one or more of the books described that is the point of these reviews. I look forward to your feedback that may be directed to me at rgj1@mac.com.
Dr. Robert G. Johnson, FCCP

From the turn of the past century emerged two men who, as it was taught in midcentury, were geniuses of the highest order. One, the inventor of the light bulb and phonograph, seemed entirely accessible, his rise from boy-telegraph operator to founder of an electrical revolution was tangible through the inventions he wrought. The other seemed less comprehensible, was an astoundingly brilliant physicist who revolutionized the world by unleashing the power of matter and the relativity of time.

Two recently published books provide an opportunity to compare these two acclaimed geniuses, contrasting what constituted their brilliance, the education that may have enhanced it, and the collaborative nature of their accomplishments. The less well-known dimension of their personal lives is also revealed lucidly and clinically.

There were many similarities between the two men born approximately 30 years apart. Both were dysfunctional fathers and less-than-doting husbands, a fact most starkly supported by Einstein's hypothecation of his (at-the-time-unawarded) Nobel prize as a means of winning a divorce from his first wife. Both were men with great mental gifts and nearly equal obstinacy. Both men's magna opera occurred in the decade that spanned their mid-twenties to mid-thirties. Both spent the last half of their long lives (Einstein died at 76 and Edison at 84) as legendary figures, pursing threads of their prior work. Edison was a man who cleverly pursued individual inventions but who then too quickly abandoned each one leaving the ultimate success, and profit, to others (the phonograph, recording, and radio are but three glaring examples). Einstein's greatest theories were the foundation for discoveries made by many brilliant physicists, while the master ignored such low hanging fruit reaching for another giant-step breakthrough, which eluded him to the end.

There were even more differences than similarities between the men. Edison was decisively a technologist and Einstein, completely a scientist. Edison was a tinkerer who improved on existing technology. Einstein's special theory of relativity was unquestionably disruptive, as disconnected as a scientific discovery can be from prior work. Einstein was born in Germany to parents with financial means (his father dabbled in the commercial generation of electricity, an Edisonian-connection), and he was educated in a classical-university tradition. Edison, by contrast, was American-born to financially less-able parents, and his education hardly included much more than a high school exposure. Perhaps the most striking contrast finds an Einstein, often pictured an aloof loner, as far more collaborative with peers, able to debate his theories with friends who were colleagues, in coffee shops and at suppers. Ever doubtful, ever searching his thirst for collaboration was enormous. The more avuncular characterized Edison, despite being a man who ran a laboratory teeming with inventions and technicians, was distinctly independent. Credited with lighting up the lives of Americans through electricity, he was darkly dismissive of dialog, criticism, and, to a great extent, doubt. While Einstein's life was marked by his Jewish-ancestry, anti-Semitism, and his flight from a Nazi regime, Edison cherished the close friendship of Henry Ford, an admirer of that same fascist regime.

As epilogue, one can note that these two books are very different to read. Stross' is, like his subject, easily accessible and quickly read. While Isaacson's more ponderous tome offers wonderfully lucid explanations of Einstein's physics and mathematics that reflect great scholarship and pedagogy on the part of the author. Interestingly, there is a synoptic moment in these biographies (Einstein: 299 and Edison: 274), when Einstein's 1921 (his Nobel laureate year) visit to Boston is recounted, inclusive of a question he was asked from the nonformally educated Edison's 150-item arcane "test" for potential employees. Einstein was asked the speed of sound, to which Einstein, who surely understood the speed of sound better than most other living humans, replied that he did not carry such information in his head, as it is readily available in books. He added, "The value of a college education is not the learning of many facts but the training of the mind to think."

At the very least, these books provoke much thought about the very nature of genius. ■

Product of the Month: Best of PCCU

In the two 2nd editions of Best of PCCU, you will find some of the best critical care and pulmonary articles from recent PCCU volumes to provide you with current information and management strategies related to the care of critically ill and pulmonary patients.

For more information and to purchase the Best of PCCU editions, please visit the ACCP Store online at www.chestnet.org.

PCCU Lessons for June 2008

► **Heparin-Induced Thrombocytopenia: Diagnosis and Treatment.** *By Dr. Jonathan M. Siner*

► **Silica-Related Lung Disease: It's Still Here.** *By Dr. Daniel E. Banks, FCCP*

PCCU Lessons for July 2008

► **New Antidotes for Poisoning and Overdose.** *By Dr. Thomas E. Kearney,*

► **Pulmonary Complications of Anti-TNF Therapy.** *By Dr. Albert J. Polito, FCCP*

NEWS FROM THE COLLEGE

AMERICAN COLLEGE OF CHEST PHYSICIANS

NetWorks Update

Allied Health

The partnership between ACCP and the National Board for Respiratory Care (NBRC) has existed for almost 50 years. The ACCP originally joined the American Association for Respiratory Care and American Society of Anesthesiologists to form the American Registry of Inhalation Therapists. The primary mission of the organization, now known as the NBRC, was to determine the competence of the respiratory therapists (RTs) emerging as essential members of the health-care team.

The NBRC has expanded and credentialed significant numbers of registered respiratory therapists (RRTs) and certified respiratory therapists (CRTs). The number of RRTs now exceeds 102,000.

In 1983, the credentialing system became a hierarchical process. The CRT examination was redesigned to assess the skills expected of RTs at their entry into practice; the two-part RRT examination also was modified to assess the advanced achievement of RTs. The content of the CRT and RRT examinations did not overlap, and the CRT credential became a prerequisite for earning the RRT designation.

These credentialing changes facilitated efforts to achieve licensure for RTs, and the NBRC offered the CRT examination for use by the states that regulate practice. All states that regulate RTs recognize the NBRC credentials as part of the licensure process. CRTs and RRTs can enjoy mobility between states, avoiding onerous requirements for retesting, and the costs of licensure are mitigated by the availability of the NBRC examinations.

The NBRC currently administers three other credentialing programs for pulmonary function technologists (certified pulmonary function technologist [CPFT] and registered pulmonary function technicians [RPFT]) and for neonatal/pediatric specialists (CRT-NPS or RRT-NPS).

NBRC examinations are offered via computer at more than 170 Applied Measurement Professional (AMP) Assessment Centers, operated by the AMP, the subsidiary of NBRC.

The NBRC is developing a specialty examination for RTs performing sleep disorders testing and therapeutic intervention; this examination will be administered in 2009. The NBRC also is evaluating the idea of offering a specialty credential for RTs practicing in adult critical care.

Contact NBRC at www.nbrc.org.

Gary Smith, RRT

Critical Care

The Critical Care NetWork is very pleased to announce that Dr. Kay Guntupalli, FCCP, will present at the Critical Care NetWork open meeting. Dr. Guntupalli is the ACCP President-Designate and recipient of the Second Eli Lilly and Company Distinguished Scholar in Critical Care award.

The steering committee is working to provide additional resources on the Critical Care NetWork Web page and requests your help in submitting interesting clinical vignettes, images, and tracings for the NetWork Online Clinical Puzzlers. Please contact LTC Alex Niven, MC, USA, FCCP, at alexander.niven@amedd.army.mil with submissions or questions. In addition, the NetWork has had primary input into the recently completed ACCP ultrasound course.

The NetWork will be represented significantly at the new airways course held this July, chaired by Dr. Niven, at the ACCP Simulation Center for Advanced Clinical Education at the ACCP in Northbrook, IL.

MAJ Alexander Niven, MC, USA, FCCP

Clinical Pulmonary Medicine

Measurement of exhaled nitric oxide is a simple noninvasive test that provides an accurate assessment of lower airway eosinophilic inflammation. It is increasingly being used in the diagnosis of asthma, as well as in monitoring response to asthma treatment. Recently, Hahn and colleagues (*Mayo Clin Proc* 2007; 82:1350) at the Mayo Clinic reported that measurement of exhaled nitric oxide accurately predicted response to inhaled corticosteroids (ICS) in patients presenting with chronic cough. Patients with an elevated exhaled nitric oxide had a strong likelihood of response to ICS, whereas a low exhaled nitric oxide virtually excluded a response to ICS. In this study, the exhaled nitric oxide test predicted the response to ICS better than methacholine challenge testing.

Compared with methacholine challenge or induced sputum, measurement of exhaled nitric oxide involves considerably less time and cost. Whereas methacholine challenge testing can be associated with potential adverse effects, such as wheezing, dyspnea, and chest pain, the exhaled nitric oxide test is a noninvasive test with little, if any, documented side effects. Although the cost of the exhaled nitric oxide analyzers has been prohibitive for many pulmonary practices, the US Food and Drug Administration has recently approved a less costly handheld device.

Use of exhaled nitric oxide may streamline how patients with chronic cough are evaluated and treated in the future.

Dr. Peter Hahn, FCCP

Cardiovascular Medicine and Surgery

In timely synchronization with the American College of Cardiology meeting in Chicago, the *New England Journal of Medicine* published ENHANCE (Effect of Combination Ezetimibe and High-Dose Simvastatin vs Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia), the double-blind, randomized controlled trial comparing the use of ezetimibe, a cholesterol absorption inhibitor, as an adjunct to baseline therapy with simvastatin, 80 mg, in patients with familial hyperlipidemia (Kastelein et al. *N Engl J Med* 2008; 358:1431). The primary endpoint in this rather short 2-year trial was the mean change in the carotid artery intima-media thickness (IMT). Despite impressive results in additional low-density lipoprotein (LDL) cholesterol-lowering (141.3+52.6 mg/dL vs 192.7+60.3 mg/dL, $p<0.01$), the group receiving simvastatin-ezetimibe therapy did not show a statistically significant difference in the primary endpoint, which was mean IMT changes (0.0111+0.0038 mm), vs the group receiving simvastatin-placebo therapy (0.0058+0.0037 mm; $p=0.29$). This result seems to "fly in the face" of the principal tenet that emerged in the treatment of coronary artery disease (CAD) and advanced atherosclerosis: the lower the LDL-cholesterol level, the better the outcome.

The result of this study could have wide-reaching implications; particularly, because it appears to be the second setback in the promising development of new ways to treat preclinical and manifest CAD. The same lead author and principal investigator for the RADIANCE 1 (Rating Atherosclerotic Disease Change by Imaging With A New CETP Inhibitor) trial showed in an earlier article (Kastelein et al. *N Engl J Med* 2007; 356:1620) that an inhibitor of cholesteryl ester transfer protein (Torcetrapib; Pfizer; New York, NY), which increased high-density lipoprotein (HDL)-cholesterol levels, and, thus, worked differently than statins, was detrimental in a similar study group also using carotid IMT measurements as the endpoint.

The limitations of this study have been discussed in a thoughtful editorial by Brown and Taylor (*N Engl J Med* 2008; 358:1504) accompanying the ENHANCE publication.

Dr. Thomas Behrenbeck, FCCP

Occupational and Environmental Health

An international team of experts has completed collaboration on the ACCP consensus statement, Diagnosis and Management of Work-Related Asthma. The consensus statement has been accepted for publication as a supplement to CHEST. In coordination with the publication of the consensus statement, materials will be posted online and include: (1) a form to assist with targeted history-taking to identify possible work-related asthma; (2) a patient information fact sheet on work-related asthma; and (3) a work information sheet for company nurses/doctors/health and safety committees.

Work conditions in some dusty trade jobs in the early part of the 20th century produced devastating pulmonary health effects from respirable silica. Simple interventions, such as personal respiratory protection and engineering control measures, can reduce occupational risk. Dr. Paul Blanc will deliver the CHEST 2008 open meeting special presentation on Monday, October 27, entitled, "Historical Aspects of Occupational Lung Disease."

Visit www.chestnet.org/networks/oeh/.

Dr. Ware Kuschner, FCCP

Continued on following page

This Month in *CHEST*: Editor's Picks

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

- **Burden of Concomitant Asthma and COPD in a Medicaid Population.** *By Dr. F. T. Shaya , et al.*
- **Combined Clot Fragmentation and Aspiration in Patients With Acute Pulmonary Embolism.** *By Dr. G. Eid-Lidt, et al.*
- **Effects of Dynamic Bilevel Positive Airway Pressure Support on Central Sleep Apnea in Men With Heart Failure.** *By Dr. M. Arzt, et al.*
- **Impaired Pulmonary Diffusing Capacity and Hypoxia in Heart Failure Correlates With Central Sleep Apnea Severity.** *By Dr. I. Szollosi, et al.*

TRANSPARENCY IN HEALTH CARE

- **Improving Handoff Communications in Critical Care: Utilizing Simulation-Based Training Toward Process Improvement in Managing Patient Risk.** *By Dr. H. Berkenstadt, et al.*

G/W EDITORIAL: The Patient Handoff: Medicine's Formula One Moment. *By Dr. W. Dunn, FCCP, et al.*

- **Acute Respiratory Infections in a Recently Arrived Traveler to Your Part of the World.** *By Dr. S. J. Gluckman*
- **Extracorporeal Membrane Oxygenation: Current Clinical Practice, Coding, and Reimbursement.** *By Dr. D. J. E. Schuerer, et al.*

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AMERICAN COLLEGE OF CHEST PHYSICIANS

NEWS FROM THE COLLEGE

Continued from previous page

Pulmonary Vascular Disease

PVD topics have been chosen for CHEST 2008, including VTE prophylaxis; collagen vascular disease; case studies in pulmonary vascular disease; sickle cell disease; health-care disparities; pulmonary hypertension in the setting of left heart disease; COPD; sleep apnea; and interstitial lung disease.

At the CHEST 2008 PVD NetWork open meeting, Dr. Karen Fagan will talk about the potential for the use of rho-kinase inhibitors in pulmonary arterial hypertension. A survey of practicing physicians has been conducted by Dr. Omar Minai, FCCP, to evaluate the care of patients who have pulmonary hypertension associated with parenchymal lung disease.

The NetWork has reviewed the Antithrombotic and Thrombolytic Therapy: ACCP Evidence-Based Clinical Practice Guidelines, Eighth Edition. Simulation sessions for right heart catheterizations, interpretations of ventilation-perfusion scans in chronic thromboembolic disease, and basic echo interpretation have been proposed for presentation at the ACCP Simulation Center for Advanced Clinical Education at the ACCP in Northbrook, IL. The PVD NetWork also is working on a collaboration between the ACCP and the Pulmonary Vascular Research Institute to enhance PVD education. Visit www.chestnet.org/networks/pvd/.

Dr. Kamal Mubarak, FCCP

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PROFESSIONAL OPPORTUNITIES

Pulmonologist

Mercy Hospital of Tiffin, located in Tiffin, Ohio, was founded more than 93 years ago on a compassionate mission of serving our patients needs. Weíve seen their need and medical technology, change dramatically through the decades. It's why we're investing nearly $60 million in our facilities and service through the Designing Our Future Project. A major part of the Designing Our Future Project is the construction of a 140,000 square foot hospital and the recruitment of a pulmonologist. The hospital will feature 67 private rooms and the most advanced technology designed to enhance the delivery of patient care. The new hospital will make it easy for patients to access the site and navigate through the facility. Plans also include enhanced outpatient service capabilities and surgery suites designed and equipped with the latest technology. If you are considering career opportunities in a safe community with wonderful schools, and an enviable quality of life and the absence of large city medical staff politics, we would like to speak with you in confidence. Inquiries, including curriculum vitae should be addressed to: Tom Leeds, Medical Staff Recruiter, Mercy Health Partners, 2200 Jefferson Avenue, Toledo, Ohio 43604 or call 1-800-837-4664, extension 3999.

Pulmonary Critical Care Opportunity
Northern California

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

SMG is a multi-specialty group of over 300+ members. SMG offers an income guarantee with shareholder track, generous compensation, benefits, and retirement package.

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

Auburn is centrally located in the Sierra Nevada foothills between Sacramento and Lake Tahoe. Auburn is close to shopping and restaurants, and offers a variety of outdoor activities.

Physician Recruitment
800-650-0625
916-643-6677 fax
develops@sutterhealth.org
www.sutterhealth.org

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SOUTHERN CALIFORNIA PULMONARY/CRITICAL CARE OPPORTUNITY

Our well-established, dynamic group is looking for BC/BE Pulmonologist/CCM Physician to join as a future partner to one of the largest, most well respected, successful pulmonary practices in the Greater Los Angeles and San Gabriel Valley areas. Join an excellent group of physicians who are life style and family oriented. Live in a great location which offers an abundance of cultural and recreational activities. This busy inpatient/outpatient practice encompasses all aspects of Pulmonary and Critical Care for great growth opportunities. Offers competitive compensation and excellent benefits leading to early, full partnership. Fax CV to: 626-795-2716 Attn: Tania or email to taniakure@yahoo.com

Marietta Pulmonary Medicine
Suburban Atlanta

Well-established, busy eleven-physician single-specialty Pulmonary practice in suburban Atlanta, Georgia, looking for one or more BC/BE Pulmonary/Critical Care physicians. Sleep certification is a plus. Practice includes all aspects of pulmonary medicine, including critical care, sleep medicine, out-patient clinic, pulmonary rehab and clinical research. Practice located at two large acute-care hospitals, with one being the busiest ER in Georgia, and also rounds at a near-by long term acute care hospital. Competitive salary with bonus potential and generous benefits package. Fax CV to: 770-792-1738.

Pulmonary/Critical Care/Sleep

West Central Florida group seeks BC/BE to join practice encompassing all aspects of pulmonary, critical care and sleep medicine, office and hospital practice. Early partnership, competitive salary and fringe benefits. Please respond with CV to Chest #74, P.O. Box 996, Abingdon, MD 21009.

BC/BE PULMONARY CRITICAL CARE

PHOENIX, AZ - BC/BE PULMONARY CRITICAL CARE - Join an established, progressive, pulmonary group with five members seeking to add a sixth. Partnership opportunity available for the right candidate. J1 OK. Fax CV to 623.523.6475 or email hresources@phoenixmedicalgroup.com

NORTH CAROLINA-NEAR PINEHURST PULMONOLOGIST

Assume private practice or be employed in family community located less than two hours from beaches, Charlotte, Raleigh and just 35 minutes from golf resort of Pinehurst. Contact Melisa Ciarrocca at 800-764-7497, Fax: 910-276-0470 or email: Melisa.Ciarrocca@scotlandhealth.org Website: www.scotlandhealth.org

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DORIBAX™

(doripenem for injection)
for Intravenous Infusion

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions: Serious and occasionally fatal hypersensitivity (anaphylactic) and 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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January 2008

10157601B

- 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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