

CHEST *Physician*

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS



COURTESY ADRIENE HUGHES

VTE prophylaxis rates rose from 50% of patients in 2005 to 98% at his institution in 2007, Dr. Gregory A. Maynard reported.

VTE Collaborative Gets Underway

BY ALICIA AULT

Elsevier Global Medical News

Hospitals that have been lagging on prevention of venous thromboembolism might find themselves increasingly at risk for lower reimbursement or downgrades in quality ratings, but a new Society of Hospital Medicine program may help some facilities start measuring up.

The Joint Commission is close to implementing a set of VTE measures looking at whether prophylaxis is in place within 24 hours of admission. The Centers for Medicare and Medicaid Services already refuses to pay for any VTE incurred as a complication of hip or knee replacement.

But these penalties have not been huge motivating factors for facilities when it comes to VTE, said Dr. Gregory A. Maynard, chief of the division of hospital medicine at the University of California, San Diego.

The biggest hurdle still seems to be the lack of physician awareness about which

populations are vulnerable, said Dr. Maynard, who has been involved in collaboratives backed by the Institute for Healthcare Improvement and the Agency for Healthcare Research and Quality. That's partly because while these events are common, an individual physician might not see many VTEs in his or her own practice, he said.

Dr. Maynard has been a key architect of the SHM's efforts to help hospitalists improve VTE prevention. The VTE Prevention Collaborative, which launches this month, is supported in part by Sanofi-Aventis U.S. Participants will have access to a toolkit, resources, and individualized mentoring and support as part of the program developed by Dr. Maynard and Dr. Jason Stein, director of the Clinical Research Program for the section of hospital medicine at Emory University, Atlanta.

According to Dr. Maynard, nearly every hospitalized patient is at risk for VTE, which includes deep vein thrombosis (DVT) and

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CPAP Not the Only Option for Sleep Apnea

Appliances, surgery, weight loss help.

BY BRUCE JANCIN
Elsevier Global Medical News

SAN ANTONIO — The days when continuous positive airway pressure was the only arrow in the quiver for physicians targeting obstructive sleep apnea are long gone.

The most popular session at the annual meeting of the Associated Professional Sleep Societies—the one whose overflow crowds brought out the fire marshals—was devoted to alternatives to CPAP that have come of age: oral appliances, maxillofacial surgery, and weight loss.

Session chair James K. Walsh, Ph.D., set the stage, citing studies showing that typically 50% of patients discontinue CPAP within 1 year. Moreover, the percentage of nights patients use their CPAP drops after a couple of months from 50% to 40% and even 30%. An average of about

3 hours of use per night is the norm in clinical practice.

“The goal is to treat sleep apnea every night throughout the night. I’m not at all trying to suggest this therapy is totally ineffective, but I would term it highly suboptimal,” said Dr. Walsh, executive director of the sleep medicine and research center at St. Luke’s Hospital in St. Louis.

While CPAP remains the guideline-recommended gold standard therapy, many patients dislike sleeping while wearing a mask, and their sleep partners often aren’t crazy about CPAP, either. Speakers at the session addressed the best-established alternatives.

Oral Appliances

This field has experienced phenomenal growth in recent years as a consequence of American Academy of Sleep

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Biologics Tied to Pulmonary Infections

BY M. ALEXANDER OTTO

Elsevier Global Medical News

PORTLAND, ORE. — Patients with suspicious, productive coughs should be worked up to rule out atypical mycobacterial infections before they are treated with tumor necrosis factor inhibitors, even if their chest x-rays and TB tests

are negative, according to Dr. Kevin Winthrop.

“These biologics seem to promote mycobacterial growth; you have to be careful an infection isn’t hiding,” he said at the Society for Pediatric Dermatology annual meeting.

Chest x-rays are not sensitive enough to pick up infection by *Mycobacterium avium* and other nontuberculous mycobacteria

(NTM), which are twice as likely to cause pulmonary infection in the United States as *M. tuberculosis* is, Dr. Winthrop of the division of infectious diseases at Oregon Health and Science University, Portland, said in a later interview.

Both chest computed tomography and sputum culture

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SLEEP
STRATEGIES

Sleep issues in
life-threatening illnesses.

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Prevention Program Expanded

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pulmonary embolism. Most patients have four to six risk factors, he said. The three big risk categories are stasis (related to age greater than 40 years, immobility, anesthesia, obesity, stroke, or heart failure), hypercoagulability (associated with cancer, sepsis, smoking, and pregnancy), and endothelial damage (surgery, central lines, trauma, or prior VTE).

Pulmonary embolism is the cause of death in more than 100,000 hospitalized patients each year, and a contributing factor in the death of approximately 100,000 additional inpatients annually, according to SHM estimates.

And yet, studies have found that only about 30%-50% of inpatients are given appropriate prophylaxis—despite the availability of guidelines and protocols that make the process more efficient and of effective pharmacologic agents. The ENDORSE trial, for instance, found that among 70,000 inpatients, only 59% of surgical patients and 40% of medical patients were given appropriate prophylaxis (Lancet 2008;371:387-94).

At UCSD, Dr. Maynard and Dr. Stein (who was previously at UCSD) leveraged

an AHRQ grant to build a protocol for VTE prevention. It was designed with the aim that it would be universally applicable to any and all hospital programs, he said. The protocol increased prophylaxis rates from 50% of patients in 2005 to 98% in 2007 at UCSD (J. Hosp. Med. 2010;5:10-8).

Essentially, it was a simple model that stratified patients into low-, moderate-, and high-risk categories. Almost no patients fall into the low-risk category; most are classified as moderate risk, Dr. Maynard said.

The risk assessment can be completed by a physician in seconds and can be done either on paper or as part of an electronic health record. Once determined, the risk level is linked to a menu of prophylaxis options, either in chart form, on paper, or electronically. Importantly, these options very specifically say which pharmacologic agents, and at what dose, are most appropriate for the patient, given the risk level and taking into account other factors. The protocol also recommends that mechanical prophylaxis only be used as an adjunct, not as a first-line therapy.

To ensure the protocol was followed, Dr. Maynard and Dr. Stein created a method they dubbed “Measurevention”—that is, the prophylaxis is monitored on a real-time basis and the intervention is done in real time, as well. The program also automatically collects data that can be used for quality improvement.

If a patient is indicated to need prophylaxis but is not identified as having received it on the medication record, the nurse or pharmacist receives an automated note. They in turn notify the physician via text message or page. About half the time, the physician changes the order, and the rest of the time, there is a valid reason for no prevention—or the physician simply does

not want to be told what to do, Dr. Maynard observed.

At Emory, the Measurevention strategy was adopted in 2009 as the final piece of the VTE prevention program, which started in 2006. Patients are color coded on a “dashboard” that is refreshed hourly. Red means no prophylaxis ordered, yellow means mechanical only has been ordered, and green means the patient is receiving a pharmacologic agent.

Six months after it was implemented, the dashboard helped pull prophylaxis rates above 90% in the 15 inpatient units at Emory University Hospital that were using the strategy, triple the rate before the dashboard, Dr. Stein said.

A year after starting the real-time monitoring in 2008, one 20-bed ICU had a 75% reduction in potentially preventable hospital-acquired VTE, “attributable to a similarly significant rise in VTE prophylaxis from 73% to 94%,” he said.

There were nine fewer clots in that unit, which “represents real morbidity prevention and real cost savings, and very possibly represents preventable deaths from pulmonary embolism,” he said.

The implementation of the dashboard—which is now available to nurses and physicians at five Emory hospitals—has created new channels of communication between clinical and information services and contributed to an increased sense of pride in frontline nurses and clinicians, Dr. Stein observed.

“Ultimately, we’ve developed a new mindset for how performance is measured and improved at Emory,” Dr. Stein said.

The SHM hopes that other facilities can replicate the Emory experience. It has enrolled 80 facilities in the Prevention Collaborative. The IHI and AHRQ also have enrolled dozens of hospitals in collaborations to reduce VTE.

Dr. Maynard said that awareness may also increase throughout the Department of Veterans Affairs, which initially had six hospitals take part in a pilot that he and Dr. Stein helped launch. Now, “many, many sites in the VA” are using the VTE prevention toolkit, he said.

VTE prophylaxis has been “suboptimal for a long time,” Dr. Maynard said. But “it’s getting there.” ■

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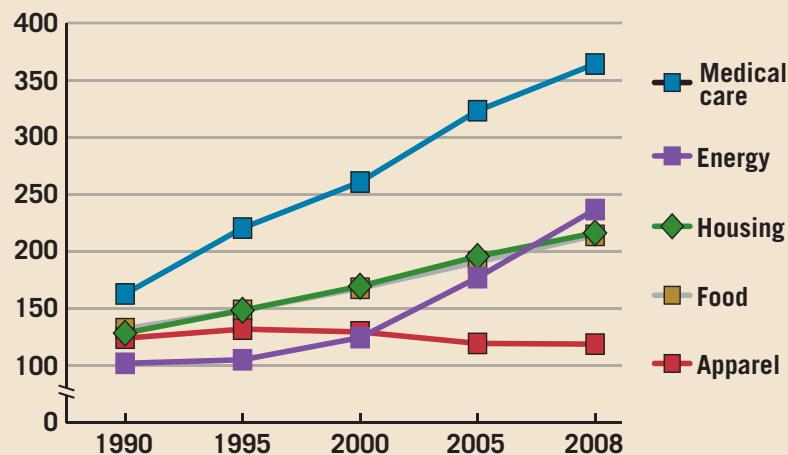
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DATA WATCH

Consumer Price Index for Medical Care Up 124% Since 1990



Source: U.S. Department of Labor

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Survival After Lung Transplant Varies by Center

BY MARY ANN MOON
Elsevier Global Medical News

Survival after lung transplantation varies widely across the 61 U.S. medical centers where it is performed, according to a report in JAMA.

However, only 15% of that variation can be attributed to the volume of procedures done at each center, said Dr. Gabriel Thabut of the department of health sciences research at the Mayo Clinic in Rochester, Minn., and his associates.

"We assessed the association of center volume and survival using different time frames, different definitions of volume, and different statistical methods. All analytic frames showed a consistent and statistically significant positive association between center volume and survival," they said. However, volume contributed only a small amount to mortality after lung transplant, and several low- and medium-volume centers achieved good outcomes, showing that "volume alone does not determine performance," they noted.

Dr. Thabut and his coinvestigators undertook their study because research has suggested that outcomes vary greatly from one center to the next. "For example, studies from several large centers report 3-year survival rates greater than 70% and even 75%—rates that far exceed the average 3-year survival of 64%" reported nationally, they said.

The researcher analyzed data from UNOS (United Network for Organ Sharing), a registry that includes all lung transplant cases since the first procedure was performed in 1987, and examined outcomes for 15,642 procedures.

Approximately 13% were done in centers that performed fewer than 10 lung transplants annually, 39% in centers that performed 10-25 annually, 41% in centers that performed 25-50 annually, and 7% in centers that performed more than 50 annually.

Thus, transplant centers varied by as much as 10-fold in the number of procedures they performed each year, the researchers noted.

Overall, median 1-month survival was 93%, 1-year survival was 80%, 3-year survival was 63%, and 5-year survival was 50%.

COMMENTARY

Dr. Joseph Barney, FCCP, comments: Despite the fact that allogeneic lung transplantation has found its way into mainstream health care in the past 20 years, it remains one of the more complex postoperative care situations in medicine. Clearly this study demonstrates that there is much more to lung transplant success than thinking that doing more makes for a better outcome. While individual surgeon expertise has relevance to transplant outcomes, far greater downstream effects on patients are felt in transplant programs without adequate ancillary staff to support these patients after they are discharged back into normal life to survive. Transplant programs without sufficient transplant coordinators to manage the numbers of patients coming out of transplant programs and their chronic medical care are fertile ground for poor outcomes, and this study might be a springboard to investigate this facet.

Survival varied markedly among the different transplant centers: In all, 1-month survival was 89%-95%, 1-year survival was 68%-85%, 3-year survival was 45%-72%, and 5-year survival was 30%-61%.

This variation in survival persisted after the data were adjusted to control for differences among transplant centers in donor selection, recipient selection, and surgical approaches. This finding "suggests that centers may exhibit true differences in the quality of care provided during or following transplantation," Dr. Thabut and his associates said (JAMA 2010;304:53-60).

"That our central results remained unchanged through a series of sensitivity analyses testing these and other potential influences therefore strengthens considerably the conclusions that can be drawn. Specifically, our results suggest that the influence of center on survival after transplantation is large and ... may be of comparable magnitude to the influence of recipient age," they wrote.

In general, survival correlated with the volume of procedures performed, with high-volume centers showing better patient survival than did medium- or low-volume centers.

However, volume accounted for only 15% of the variability among centers, and that variability remained strongly significant after the volume of procedures was controlled for.

Survival rates were most varied during the first year after transplant, then tended to become similar across transplant centers. This suggests that "there may be undue variability in centers' perioperative and early postoperative practices." It also indicates that "differences in surgical expertise might contribute to center variability," the researchers said.

Unfortunately, the UNOS data were not sufficient to distinguish between a "center effect" and a "surgeon effect" on survival, because the registry does not include surgeon identities or practice characteristics that would indicate the surgeon's level of expertise.

The study findings suggest that it might be possible to identify specific practices that favor survival at high-performing centers, so that low-performing centers can adopt those practices and improve their outcomes.

"The fact that some low-volume centers achieve good outcomes ... suggests that excellence in lung transplantation is not merely a 'practice makes perfect' phenomenon," Dr. Thabut and his colleagues said.

In the meantime, clinicians may want to provide patients with center-specific outcome data so they can make more informed decisions as to which transplant center to attend. This information could be particularly important to patients who have conditions that benefit only modestly from lung transplantation, such as chronic obstructive pulmonary disease. "For such patients, the choice to be listed for transplantation or not could be sensitive to even moderate differences in the expected outcomes among local centers," the researchers said.

Dr. Thabut was supported by AstraZeneca and the Public Assistance Hospital of Paris, and an associate was supported by the Agency for Healthcare Research and Quality. The remaining coauthors reported no relevant disclosures. ■

Endoscopic Lung Cancer Staging Is Fast, Effective

BY BRUCE JANCIN
Elsevier Global Medical News

KEYSTONE, COLO. — Endobronchial and esophageal ultrasound-guided needle aspirations will emerge as the primary method for staging lung cancer patients, according to Dr. Ali I. Musani, FCCP.

The approach is used "at all the top-notch centers in the country [and] allows you to get to just about every node. You lay the patient down and complete the entire staging within 1 hour under conscious sedation in one room," Dr. Musani said at a meeting on allergy and respiratory disease sponsored by National Jewish Health, Denver.

Guided by real-time endoscopic ultrasound, the combined endoscopic dual needle sampling method offers significant advantages over the various surgical methods of staging—thoracotomy, mediastinoscopy, and video-assisted thoroscopic surgery (VATS)—all of which are inpatient procedures that require general anesthesia and are thus far more expensive.

In addition, VATS and thoracotomy entail considerable morbidity. Mediastinoscopy has a serious complication rate of less than 1%, but has a lengthy list of relative contraindications.

And in an influential prospective crossover trial, endobronchial ultrasound-guided transbronchial needle aspiration had a higher diagnostic yield

THE DOWNSIDE OF MINIMALLY INVASIVE STAGING PROCEDURES IS THE LIMITED NUMBER OF PULMONOLOGISTS WITH TRAINING AND EXPERIENCE.

than mediastinoscopy in pathologic staging of lung cancer (J. Thorac. Oncol. 2008;3:577-82).

Endobronchial ultrasound-guided transbronchial needle aspiration provides excellent access to the superior mediastinal, subcarinal, and N1 lymph nodes. Esophageal ultrasound-guided

fine-needle aspiration offers ready access to the left lower paratracheal, subaortic, and inferior mediastinal nodes.

The two procedures are complementary and together provide better diagnostic accuracy than either alone, said Dr. Musani, director of interventional pulmonology at National Jewish Health.

The latest development in minimally invasive lung cancer staging technology is combined endobronchial ultrasound-guided/esophageal ultrasound-guided needle aspiration performed through a single dedicated linear endobronchial ultrasound bronchoscope performed by a single operator as an outpatient procedure.

German investigators recently reported that this approach had a sensitivity of 96% and a negative predictive value of 95% in a study involving 150 consecutive patients with a presumptive diagnosis of non-small cell lung cancer. That was a better performance than with either approach alone. There were no complications (Chest 2010 Feb. 12; doi:10.1378/chest.09-2149).

The downside of these minimally invasive, high-yield staging procedures is the limited number of pulmonologists with the training and extensive experience required to become facile at using them, according to Dr. Musani.

The 7th edition of the American Joint Committee on Cancer Staging Manual is now in effect. The new staging system for non-small cell lung cancer contains significant changes in the tumor (T) and metastasis (M) components, but no changes to the node (N) component.

Dr. Musani disclosed that he serves on the speakers bureaus for Cardinal Health, Olympus, and SuperDimension Ltd. ■

COMMENTARY

Dr. W. Michael Alberts, FCCP, comments: While this is clearly an advance with impressive potential, it is important to stress that there is a significant "learning curve" to achieving sensitivities and negative predictive values reported in the literature.

Thinking Outside the Mask

Sleep Apnea • from page 1

Medicine guidelines recommending the devices for mild to moderate obstructive sleep apnea (OSA).

"For physicians, this is a particularly confusing field. There are more than 100 oral appliances on the market, and I've seen another 4 new ones introduced at this meeting. There's a lot of heavy marketing going on," said Dr. Alan A. Lowe, professor of oral health sciences and chair of the division of orthodontics at the University of British Columbia, Vancouver.

Not all of the devices have been approved by the Food and Drug Administration, and only seven are backed by clinical trials data. No single device is right for all patients, and the best results are achieved with devices that are adjustable in all planes in space, he stressed.

"The titration of an oral appliance is essential, and it takes weeks to months," Dr. Lowe said. "You don't just send patients home with a 'boil and bite' device and say, 'Okay, off you go.' You need to go through the titration phase. So physicians who are prescribing oral appliances and just giving them to their patients might as well give them CPAP with a pressure of 7 mm Hg and send them home and tell them to wear it. It's absolutely useless to do that."

Oral appliances that have been subjected to formal trials typically show roughly an 80% success rate in patients with a baseline apnea-hypopnea index (AHI) below 30 episodes per hour, with the success rate dropping off to 60% in those with more severe OSA.

"Oxygenation improvement is always greater with CPAP because it forces air into the lungs. Oral appliances simply

make the tube bigger and take away the obstruction," he explained.

Device titration needs to be done by a skilled dentist. The American Academy of Dental Sleep Medicine has roughly 1,600 dentist members and is a useful resource for physicians seeking a local dentist experienced with oral appliances.

The main side effect associated with oral appliances is that they cause subtle tooth movement. In a series of 70 patients with full polysomnograms and dental records, Dr. Lowe found that only 10 had no change in dentition over time. Of the other 60 patients, 29 had favorable changes in the fit and function of their teeth, whereas 31 had unfavorable changes.

"When we weigh tooth movement against adequate oxygen to the heart, tooth movement loses. I'm trying to train the profession to think that way—panic less about tooth movement and think more about what the treatment is doing for the sleep-disordered breathing," Dr. Lowe said.

Besides, his 3-year study of patients using classic CPAP masks showed that they, too, cause quantifiable changes in tooth position over time, he added.

Maxillofacial Surgery

Maxillomandibular advancement is a big operation, and it yields big results, said Dr. Kasey Li of Stanford (Calif.) University.

He cited a recent meta-analysis involving 627 patients who underwent maxillomandibular advancement (MMA). Their mean AHI dropped from 63.9 to 9.5 events/hour. Treatment success, defined as an AHI below 20, occurred in 86% of

patients. A surgical cure, meaning an AHI below 5, was obtained in 43% of patients (Sleep Med. Rev. 2010 [doi:10.1016/j.smrv.2009.11.003]).

This parallels Dr. Li's personal experience, which includes 302 patients with pre- and post-MMA sleep data. The operation typically takes about 3 hours, with a 2- to 3-day hospital stay and return to work in 4-5 weeks.

As in the meta-analysis, there have been no postoperative deaths in Dr. Li's own series. The most common side effect is cranial nerve paresthesia, which typically resolves within 6-12 months. Four of Dr. Li's patients had severe malocclusion requiring revision surgery.



'The titration of an oral appliance is essential, and it takes weeks to months.'

DR. LOWE

Ninety percent of patients report being satisfied with their results.

A multivariate regression analysis done as part of the meta-analysis identified four significant predictors of increased likelihood of MMA success: younger age, lower body mass index, less severe sleep apnea, and greater degree of maxillary advancement. This mirrors Dr. Li's experience as well.

When asked if it makes sense to perform a less morbid soft tissue surgical procedure such as tonsillectomy or uvulopalatopharyngoplasty as a first-line operation for moderate to severe OSA, reserving MMA for the nonresponders,

Dr. Li's answer was emphatically no. "The data over the past 10 years are very clear that patients with severe sleep apnea are not going to respond very well to soft tissue surgery, period. I tell patients that unless they're going to have MMA, they shouldn't bother with surgery."

A prospective study comparing MMA to CPAP is being planned at Stanford.

Weight Loss

Too many physicians are jaded about this well-established but seriously underused treatment for OSA, said Dr. Ronald R. Grunstein, professor of sleep medicine at the University of Sydney.

"I think we need to have a less nihilistic view about weight loss. We in sleep medicine are often still thinking very much in silos," he said.

Dr. Grunstein was first author of a large study with a 2-year follow-up that showed bariatric surgery to be a highly effective treatment for OSA in obese patients (Sleep 2007;30:703-10). In addition, recent studies conducted in Finland (Am. J. Respir. Crit. Care Med. 2009;179:320-7) and Sweden (BMJ 2009;339:b4609) have shown substantial improvement in OSA with weight loss achieved through a very-low-calorie diet plus exercise followed by a maintenance diet.

Promising pharmacologic alternatives to CPAP are also in development, and not all are weight-loss drugs.

Dr. Lowe disclosed that he is the inventor of the Klearway oral appliance, the royalties for which are assigned to the University of British Columbia, where they pay for much of his research. Dr. Walsh is a consultant to Ventus Medical, which markets the Provent sleep apnea therapy device. Dr. Li and Dr. Grunstein reported no financial conflicts. ■

CPAP Therapy Can Reduce Cardiovascular Risk in Apnea

BY CRAIG GUILLOT
Elsevier Global Medical News

NEW ORLEANS — Continuous positive airway pressure can reduce the incidence of cardiovascular events and hypertension in people with obstructive sleep apnea but no daytime sleepiness, according to results of a randomized study of 724 patients.

Dr. Ferran Barbé Illa of Hospital Arnau de Vilanova in Lleida, Spain, and colleagues at 14 university hospitals in Spain selected patients with an apnea-hypopnea index (AHI) greater than 20 and an Epworth sleep scale (ESS) score less than 10. The team randomized 358 of these patients to receive CPAP treatment and 366 to conservative treatment, which consisted of advice on weight control and sleep.

The researchers followed the patients for 4 years, tracking new diagnoses of hypertension and cardiovascular events, including angor pectoris, cardiac arrhythmia, peripheral ischemia, and stroke. Each patient was evaluated at 3, 6, 12, 24, 36, and 48 months.

During that time, the participants

experienced 58 cardiovascular events and 148 new cases of hypertension. Patients who used CPAP for at least 4 hours per night had 25% less risk of these outcomes than did patients receiving conservative treatment, the researchers reported at an international conference of the American Thoracic Society.

Among participants who entered the study with hypertension and received CPAP, the risk of a cardiovascular event was half that of hypertensive counterparts who were not randomized to CPAP.

This is the first randomized study showing a positive effect of CPAP on cardiovascular disease in people with obstructive sleep apnea, Dr. Barbé Illa said.

CPAP is the standard treatment for patients with daytime sleepiness. But not all people with the nighttime disorder suffer daytime sleepiness, and the benefit of CPAP for them has not been clear. Obstructive sleep apnea affects about 10% of the U.S. population and is often associated with cardiovascular disturbances.

Dr. Barbé Illa disclosed that the study was supported by SEPAR, the Instituto De Salud Carlos III (FIS), and ALLER. ■

Over Half of U.S. Adults Report Sleep-Disordered Breathing

BY BRUCE JANCIN
Elsevier Global Medical News

SAN ANTONIO — More than 20 million American adults report snoring, gasping, or stopping breathing while asleep more than 3 nights per week.

Furthermore, in excess of 100 million adults report snoring an average of more than 3 nights per week, according to the first study of the prevalence of sleep-disordered breathing symptoms in a representative sample of U.S. adults.

"More than one-half of U.S. adults report symptoms of sleep-disordered breathing, but fewer than 4% report being told by a health professional that they have sleep apnea. These findings suggest that sleep-disordered breathing may be underdiagnosed and -treated in the U.S.," Aaron D. Laposky, Ph.D., concluded at the annual meeting of the Associated Professional Sleep Societies.

He presented an analysis of data from the National Health and Nutrition Examination Survey (NHANES). The 2005-2006 and 2007-2008 versions included questions pertaining to sleep-disordered breathing symptoms.

The analysis included 4,009 men and 3,862 women. Half reported snoring more than 3 nights per week. The prevalence of this symptom of sleep-disordered breathing was 58% in men and 41.5% in women, according to Dr. Laposky of the National Heart, Lung, and Blood Institute.

Snoring, gasping, or stopping breathing while sleeping on more than 3 nights per week was reported by 13.3% of men and 7.9% of women. Extrapolating from these results to the U.S. population as a whole, as NHANES was designed for, suggests that more than 20 million adults have symptoms of sleep apnea. Rates were higher among men than among women across all age groups.

The prevalence of self-reported snoring in combination with gasping rose with increasing body mass index. Among individuals with a BMI of 30 kg/m² or greater, the prevalence was 71.6% in men and 60.6% in women.

The combination of sleep-disordered breathing plus excessive daytime sleepiness was reported by less than 1%.

Dr. Laposky reported having no relevant financial conflicts. ■

Insomnia Increases Risk of Death

BY BRUCE JANCIN
Elsevier Global Medical News

SAN ANTONIO — Chronic insomnia is an independent risk factor for all-cause mortality, conferring a threefold increased risk, according to data from the landmark Wisconsin Sleep Cohort Study.

This surprisingly robust increased risk was seen across all the major subtypes of chronic insomnia, including frequent difficulty in falling asleep, repeated awakening during the night, and waking up too early, Laurel A. Finn reported at the annual meeting of the Associated Professional Sleep Societies. Higher mortality also was seen for sleep maintenance insomnia marked by difficulty in getting back to sleep after awakening, she said.

These findings boost the priority level for treatment of chronic insomnia. The data provide added impetus for physicians to prescribe effective treatments for patients who complain of insomnia, even in the absence of comorbid medical or psychiatric conditions, added Ms. Finn of the University of Wisconsin, Madison.

She reported on 2,242 Wisconsin state employees, mean age 44 years, who completed at least two of the detailed sleep questionnaires mailed by investigators in 1989, 1994, and 2000. If on two or more surveys they reported insomnia symptoms more than five times in the prior month, they were classified as having chronic insomnia.

By this definition, 46% of participants had chronic insomnia. Chronic repeated awakening was reported by 26% of participants, while each of the other three subtypes of chronic insomnia occurred in 15%-18%.

A total of 128 participants died during a mean follow-up of 19 years. The all-cause mortality rate was 8.6% in participants with chronic insomnia and 2.6% in those with no insomnia.

In a multivariate analysis adjusted for potential confounders, including age, gender, smoking, sleep-disordered breathing, alcohol use, asthma, cardiovascular disease, diabetes, and depression, chronic insomnia remained independently associated with a threefold increased risk of mortality. Each of the insomnia subtypes was associated with a 2.5- to 3.3-fold increased risk.

Possible explanations for the increased mortality among individuals with chronic insomnia include the well-documented increased accident rates associated with chronic insomnia. Chronic sleeplessness also could hamper recovery from major illness or injury, she observed.

The Wisconsin Sleep Cohort Study is funded by the National Institutes of Health. Ms. Finn reported having no financial conflicts. ■

Geoffrey Chupp, MD, (left), Jack Elias, MD, and Lauren Cohn, MD, in the Winchester Chest Clinic.



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Anti-TNFs Up Lung Infection Risk

Biologics • from page 1

are typically needed in order to make the diagnosis.

Adalimumab, etanercept, and infliximab are indicated for plaque psoriasis; those and other TNF inhibitors have been tried off-label for many additional ailments with dermatologic manifestations, including Behçet's disease, Crohn's disease, dermatomyositis, and

tissue, 9% bone and joint, and 8% disseminated. There was one eye infection; overall, *M. avium* caused half of the infections (Emerg. Infect. Dis. 2009;15:1556-61).

Most of the patients were older women being treated for rheumatoid arthritis; only a few of the cases were associated with psoriasis therapy, but TNF inhibitors were not indicated for psoriasis during most of the study period.

Seventy-three infections included in the MedWatch database were associated with infliximab, 25 with etanercept, and 7 with adalimumab.

"Use of infliximab may pose a greater risk for NTM disease. If true, the risk could be caused by the drug itself or differences in the characteristics of patients given infliximab relative to users of the other anti-TNF-alpha compounds," Dr. Winthrop and his colleagues wrote.

"Infliximab users were more likely to be concomitantly using methotrexate at the time of diagnosis," they said.

During his presentation at the annual meeting, Dr. Winthrop said he suspects the number of anti-TNF-associated NTM infections is "much lower" in psoriasis than in rheumatoid

arthritis, which can affect the lungs and increase susceptibility to opportunistic infection by nontuberculous mycobacteria, which are ubiquitous in soil and water.

He and his colleagues noted in their report, however, that MedWatch—a voluntary reporting system—likely underestimated the incidence of TNF blocker-associated NTM infection.

A large, epidemiologic safety study of TNF inhibitors and other biologics is underway, and should further define the risks of NTM infections, said Dr. Winthrop, a coinvestigator in the project. Results could begin to be published in 2011.

He said *M. avium* is most likely to infect the lungs, while *M. abscessus*, *M. chelonae*, *M. marinum*, and *M. fortuitum* are more likely to infect skin and soft tissue.

M. kansasii is a likely pathogen of both skin and lung in the southern United States, he said.

As with pulmonary infections, NTM skin infections are difficult to diagnose; diagnosis of the skin infection typically requires a punch biopsy along with a culture or polymerase chain reaction analysis.

NTM infections do not typically respond to antibiotics used to target tuberculosis; other antibiotics must be used in combination, Dr. Winthrop said.

Pulmonary infections typically are treated for 18 months, a longer treatment course than the course for tuberculosis, because NTM infections are less susceptible to antibiotics in general.

Dr. Winthrop said that he has no relevant financial conflicts of interest to report. ■

THE MEDWATCH DATABASE INCLUDES 105 ANTI-TNF THERAPY-ASSOCIATED NTM INFECTIONS BETWEEN 1999 AND 2006; 56% WERE PULMONARY.

scleroderma (J. Cutan. Med. Surg. 2005;9:296-302).

Black boxes on product labels warn that TNF inhibition increases the risk of tuberculosis, but the risk of developing an NTM infection is not similarly emphasized.

Dr. Winthrop and his colleagues identified 105 anti-TNF therapy-associated NTM infections in FDA's MedWatch database between 1999 and 2006; 56% were pulmonary, 26% skin and soft

COMMENTARY

Dr. Jeana O'Brien, FCCP, comments: Dr. Winthrop's presentation brings further attention to a condition familiar to most practicing pulmonary physicians: NTM disease. Although appreciated for decades as a potential etiology for cough, the overall incidence of NTM disease and colonization is still poorly understood. Diagnosis of opportunistic mycobacteria is made by repeated isolation and

identification of the pathogen with compatible clinical and radiologic features.

As TNF blockers and other biologic therapies develop further indications for use, there is a definite need for increased attention to the presence of NTM. Findings of the epidemiologic safety study should provide useful information to guide evaluation of patients under consideration for these therapies.

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Promising New Drugs on Horizon for H1N1 Virus

BY BRUCE JANCIN
Elsevier Global Medical News

VAIL, COLO. — Much-needed help in treating pandemic 2009 H1N1 influenza may be on the way, with two promising investigational drugs that could become commercially available in the next several flu seasons.

Favipiravir and laninamivir are both performing well in phase III clinical trials abroad, Dr. Adriana Weinberg said at the annual conference on pediatric infectious diseases sponsored by the Children's Hospital, Denver.

Favipiravir is an oral RNA polymerase inhibitor that is effective against both influenza A and B and against other RNA viruses. It is in phase III testing in Japan. Importantly, it has no cross-resistance with the neuraminidase inhibitors or adamantanes.

Laninamivir is an inhaled neuraminidase inhibitor. The drug has an extremely long half-life such that a single inhalation constitutes an entire course of treatment. Laninamivir is effective against oseltamivir-resistant isolates. It is in phase III trials in Australia, where it is establishing a very favorable safety profile, according to Dr. Weinberg, professor of medicine, pediatrics, and pathology of the University of Colorado, Denver, and medical director of the clinical virology laboratory at University of Colorado Hospital.

Current treatment options for pandemic H1N1 flu are limited, so these two new drugs are badly needed, she added.

More than 90% of H1N1 isolates from the 2009 pandemic were resistant to adamantanes. Only the oral neuraminidase inhibitors oseltamivir (Tamiflu) and the inhalation-only formulation of zanamivir (Relenza) were available at the beginning of the pandemic.

These were supplemented by intravenous peramivir, a drug that was in phase III trials but was decreed available for use in critically ill patients as a result of an Emergency Use Authorization that was terminated in June 2010. Peramivir

has a resistance profile and efficacy similar to those of oseltamivir. Thus, its sole advantage is that it can be given intravenously.

The recommended dosing for peramivir is 6 mg/kg in neonates, 8 mg/kg for infants aged 31-90 days, 10 mg/kg for 91- to 180-day-olds, 12 mg/kg for children aged 181 days through 5 years, 10 mg/kg for 6- to 17-



Current treatment options for pandemic H1N1 flu are limited, so these new drugs are badly needed.

DR. WEINBERG

year-olds, and 600 mg for patients aged 18 years and older. The infusion is given over 30-60 minutes.

Intravenous zanamivir became available on a compassionate use basis during the pandemic. Unlike peramivir, it is effective against oseltamivir-resistant isolates.

Ribavirin does have in vitro activity against influenza, and although it's not a very good anti-influenza drug by itself, it may have a future in combination therapy for severe pandemic H1N1 disease.

Combo therapy with neuraminidase inhibitors, ribavirin, adamantanes, and interferon was widely used for avian influenza A(H5N1), but in the absence of controlled trial data, it is unclear whether the combinations enhanced efficacy.

In animal models, two drugs for pandemic H1N1 disease are more effective than one, provided that the virus is susceptible to both drugs.

Results thus far are conflicting when the virus is resistant, according to Dr. Weinberg.

Oseltamivir performed well last season against pandemic H1N1. When started within 2 days following symptom onset, it reduced mortality by 50%. It also reduced the duration of symptoms.

There is some evidence that if the drug is given within the first 3 days, it reduces viral shedding from 14 days without treatment to 7 days for seasonal influenza.

Oseltamivir was effective at limiting disease transmission during outbreaks in nursing homes and other closed communities.

Under an Emergency Use Authorization issued during last year's pandemic, oseltamivir became available for the treatment of patients of all ages with H1N1 flu.

Recent interim data from a National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group trial suggest the best dose of oseltamivir in infants is 3 mg/kg for each twice-daily dose. In premature babies, the optimal dose appears to be 1 mg/kg for each twice-daily dose (J. Infect. Dis. 2010;202:563-6).

During last year's pandemic, the World Health Organization recommended that the standard 75-mg b.i.d adult and adolescent dose of oseltamivir could be doubled in severe cases of H1N1 disease, an announcement Dr. Weinberg dismissed as "weirdness that made little sense" since the pharmacokinetics of the drug are linear up to 500 mg/dose.

Her advice: Consider quadrupling the standard dose in severe cases.

Prophylactic administration of oseltamivir is a common inducer of resistance in immunocompetent patients, which is why the WHO recommends not using the drug for prophylaxis.

Resistance also develops quickly in lung transplant recipients.

There was concern among the medical community that oseltamivir resistance would spread, but that did not happen during the past flu season. All documented cases of oseltamivir resistance occurred in patients on the agent or in close contacts of patients who were treated with the drug, according to Dr. Weinberg.

Two recent animal studies reached opposite conclusions regarding the pathogenicity of oseltamivir-resistant H1N1 strains.

One study showed the drug-resistant strains were less pathogenic than wild-type virus, whereas the other study found that the drug-resistant and wild-type viruses had similar pathogenicity.

Clearly, more work is needed in this area, she noted.

Dr. Weinberg disclosed serving as a consultant to MedImmune, Astellas, GlaxoSmithKline, and Merck. ■

FDA Warns of Pneumonia Danger With Daptomycin

The Food and Drug Administration is warning physicians and patients that the intravenous antibiotic daptomycin has been associated with an increased risk of eosinophilic pneumonia.

Daptomycin (Cubicin), a once-daily drug, is approved for complicated skin and skin structure infections caused by gram-positive bacteria such as *Staphylococcus aureus* (including methicillin-resistant strains) and for treatment of *S. aureus* bloodstream infections, including infective endocarditis.

The FDA said a review of published case reports and postmarketing adverse event reports turned up seven cases of eosinophilic pneumonia between 2004

and 2010 that seemed to be associated with use of daptomycin.

The agency is asking daptomycin manufacturer Cubist Pharmaceuticals to add new warnings to the drug's label about the increased potential for developing eosinophilic pneumonia. The condition is rare but can lead to progressive respiratory failure and death if not recognized and treated, according to the FDA. Symptoms to watch for include fever, cough, shortness of breath, or difficulty breathing. The FDA urged patients taking daptomycin who have those symptoms to immediately talk with their physician.

—Alicia Ault

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PRESIDENT'S REPORT

The Silent Force: The Ambassadors Group

Volunteering. Educating. Networking.

In the 75-year history of the ACCP, some milestones have given a broader dimension to the organization.

Through the energies and passions of the ACCP members, their spouses, and other family members, the 10-year old Ambassadors Group has provided an enormous resource to the ACCP and The CHEST Foundation.

History and Major Milestones

2000-2001: *Cindy Johnson, Chair*

► The "Ambassadors Group" was formed as a volunteer group to promote the activities and mission of The CHEST Foundation in local communities worldwide, utilizing the talents of ACCP spouses and other family members, as well as ACCP members themselves, who would attend the ACCP meetings. Cindy Johnson served as the inaugural Chair and organized the group, leading effective meetings and hosting an introductory luncheon with a guest speaker at the 2001 spring meeting. She cultivated the original leadership and members.

2001-2002: *Judi Braman, Chair*

► Judi Braman helped develop the "focus areas" for the group that parallel The Foundation's four focus areas. In the area of tobacco prevention and cessation, the Ambassadors Group adopted the Foundation's Lung LessonsSM—an educational program for elementary school students.

► To emphasize The Foundation's commitment to end-of-life care, the Ambassadors Group, under the leadership of Co-Chairs Rosemary Bone Mason and Norine Lever, created *Stories at the End of Life*, designed to promote communication between physicians and patients and their families. A call for "stories at the end of life" was published in "Parade" magazine, which resulted in the creation of six themed booklets of stories and poems, with a forward written for each by an ACCP member.

2002-2003: *Pushpa Prakash, MD, Chair*

► Pushpa Prakash helped initiate the Ambassadors Group's first membership drive.

► The *Stories at the End of Life* project was completed, with final selections from a total of over 400 stories received. Co-Chairs Rosemary Bone Mason and Norine Lever received an honorary Humanitarian Award from The CHEST Foundation for their work on this series. They worked with members of the ACCP Publications Committee, End-of-Life Care NetWork, and The CHEST Foundation. The Ambassadors Group raffle netted \$6,500 to support children's lung health initiatives.

► The Ambassadors Group annual open meeting guest speaker, Judith Mackay, MB, ChB, Director, Asian Consultancy on Tobacco Control & Senior Policy Advisor to the World Health Organization, provided a

description of "Targeting Women in Developing Countries: The New Speakers Kit—Asian Version."

2003-2004: *Diane Irwin, RN, Chair*

► Under the leadership of Diane Irwin, the first edition of the Handbook of Guiding Principles was approved, to define and formalize a structure and processes for the functioning of the group, including the establishment of committees (including membership, communications, hospitality) reporting to the Ambassadors Group leadership. These guiding principles included a mission and vision, delineated roles and responsibilities, project approval processes, and measures of success.

► The membership voted to initiate a project to promote tobacco cessation and prevention in schools, both nationally and internationally. Although open to all ACCP members and their family members, membership dues were requested and set at \$35 per person; however, members were and still are entitled to reduced rates for the cultural outings and other activities of the Ambassadors Group.

2004-2005: *Susan Kvale, Chair*

► The first annual Global Outreach Tea was held during CHEST 2004 with 30 attendees representing 11 countries.

► Susan formalized a Youth Subcommittee for high school and college-aged students and had several members joining (dues were set at \$10). Due to school schedules, these youth Ambassadors were rarely able to attend meetings at CHEST or spring or summer board meetings with their parents. However, there are currently several youth Ambassadors who are active in their local communities. The Past Chairs Council was created to be the strategic planning advisory group.

► The second Global Outreach Tea in 2005 was a success, topping the previous record with 58 people representing 13 countries and 16 states.

► The keynote speaker was Lorraine Greaves, PhD, who spoke about her work with INWAT, a voluntary International Network of Women Against Tobacco, and ICEBERGS, Interdisciplinary Capacity Enhancement: Bridging Excellence in Respiratory Disease and Gender Studies.

► The tobacco prevention program in local communities began with the first presentations based on The CHEST Foundation's Lung Lessons.SM

► The first walk/run at a school in Milwaukee, WI, was held by Monir Almassi, RN, who used the opportunity to teach the students tobacco prevention messages.

► The CHEST Foundation legally trademarked the phrase "Love Your Lungs®" for use by the Ambassadors Group for a poster contest and other projects.

► The Ambassadors Group Love Your Lungs® wristbands were produced and sales began. Oprah's "O" Magazine carried the wristband and indicated where it could be purchased.



2005-2006: *Debra Alberts, Chair*

► Debra Alberts set into motion the founding concept of an Ambassadors Group award for a humanitarian project. This award was to be funded from direct donations and the sales of products.

► Dr Salim Surani, FCCP, was introduced as the first Ambassadors Group

Humanitarian award winner. Dr Surani's project, Antitobacco Campaign, provides antitobacco education from kindergarten to third grade for children attending schools in the Corpus Christi, TX, area, using the *Ant E Tobacco* cartoon CD and book developed by Dr Kay Guntupalli, FCCP, for The CHEST Foundation. Dr Surani has educated over 20,000 elementary school students in Texas.

► Dr LeRoy M. Graham, FCCP, spoke at the annual open meeting about his project, "Not One More Life," to reach out through the African-American



Dr Jay Guntupalli (right), 2009-2010 Ambassador Group Chair, visits with member Dr Sabiha Raof, FCCP, at CHEST 2009.

churches and address the underserved populations with asthma and other respiratory conditions in Atlanta, GA.

► The position of Treasurer was added to the organization structure and guiding principles.

► Over 2,000 students were educated using the Ambassadors Group tobacco prevention programs in Guatemala, Romania, Turkey, China, and Poland, as well as in Michigan, Wisconsin, Connecticut, Florida, Alaska, California, Indiana, and New York.

2006-2007: *Cindy Johnson, Chair*

► Cindy strived to improve the financial viability of the group. Annual dues

were increased to \$50 for US members but kept at \$35 for international members and \$10 for youth members.

► Susan Kvale, Kathy Wilder, and Monir Almassi demonstrated how to present the Lung LessonsSM tobacco education program to a group of students at CHEST 2007 in Chicago. This program was videotaped for the creation of a train-the-trainers program later called Lung LessonsSM. A Presenter's Guide, used in conjunction with The Foundation's *Make The Choice: Tobacco or Health?* CD-ROM.

► It was estimated that about 7,500 students were reached with tobacco education presentations in the United States and around the world.

► The Ambassadors Group members continued to fund the Humanitarian Awards Program with their donations for one \$5,000 award each year.

► The Global Outreach Tea continued to achieve popularity, with 40 people attending from 9 countries and 17 states. Al Keith, RRT, spoke about the CTK Clinical Consultants, which delivers clinical education to empower patients to improve their health and wellness, while also emphasizing communication with physicians.

2007-2008: *Zorita Thomas, Chair*

► Zorita showcased Lung LessonsSM: A Presenter's Guide at the Women's Health NetWork luncheon, and it was posted online for accessibility and outreach to Ambassadors and non-Ambassadors.

► The CHEST Foundation began a new Lending Library, allowing Lung LessonsSM presenters to take out the materials on loan.

► More than 9,500 students were now educated in tobacco prevention since the inception of this program.

► The ACCP initiated a registration fee for guests attending the annual CHEST meeting. Ambassadors Group members whose dues were current as of October 1, 2008, were provided complimentary guest registration at CHEST 2008. This member benefit has remained in effect ever since.

► The 2008 Humanitarian Award winner was Dr G. Lakshmipathi, FCCP, from Coimbatore, India, with a project called "Say 'No to Tobacco' Educational Project Addressing School Children." Using the *Evils of Tobacco* CD in the native language, Tamil, developed by Dr Kay Guntupalli, FCCP, for The CHEST Foundation, Dr. Lakshmipathi reached over 100,000 high-school students.

► In Alaska, Kathy Wilder initiated a train-the-trainers program to provide information and resources to the school nurses and teachers, so they could continue to offer the Lung LessonsSM curriculum.

► The Ambassadors Group 2007 Humanitarian Award winner, Dr Archana Mishra, FCCP, presented her

Continued on following page

New ACCP President To Be Welcomed at CHEST 2010

Dr David Gutterman, FCCP, will be inaugurated as the 72nd ACCP President during the Opening Ceremony at CHEST 2010 in Vancouver. He is the Northwestern Mutual Professor of Cardiology and Senior Associate Dean for Research at the Medical College of Wisconsin in Milwaukee. He matriculated from the University of North Carolina at Chapel Hill with BA and MD degrees and completed a residency and chief residency in Medicine at the University of Iowa. After completing a cardiology fellowship at the University of Iowa, Dr Gutterman joined the faculty at Iowa, later moving to the Medical College of Wisconsin. Dr Gutterman's service to the ACCP has included membership on the Education and Government Liaison Committees. He has chaired the Health and Science Policy Committee and continues to serve as the ACCP representative to the executive committee of the antithrombotic guidelines panel. He has also participated as Chair of the Cardiovascular Medicine and Surgery NetWork, served as an ACCP Regent-at-Large, and beginning in January 2011, he will serve as a *CHEST* Associate Editor.



DR DAVID GUTTERMAN, FCCP

and coordination to maintain lines of communication and functional efficiencies to achieve the College's goals. My plan is to maintain our premier status as the leader in cardiopulmonary, critical care, and sleep medicine through greater internal cooperation and coordination, integrating existing activities to create new opportunities for growth, and harmonizing our relationships with sister organizations to further our mission. Accomplishing this will put us in the best possible position to support the needs of our members and facilitate their efforts toward patient-focused care.

What do you consider to be the greatest strengths of the ACCP, and how will you build upon these during your Presidency?

The ACCP is the undisputed world leader in providing quality education for cardiopulmonary caregivers. From our state-of-the-art simulation technology, our leadership in ICU telemedicine, our premier status in generating evidence-based clinical practice guidelines, and our highly acclaimed board review courses, to our annual CHEST meeting and award winning *CHEST* journal,

no organization can lay claim to such a comprehensive set of tools for promoting excellence in training and continuing education geared at improved care delivery. It is my goal to add to this repertoire several new devices for monitoring performance, instituting best practices, teaching new techniques, improving access to educational opportunities, and facilitating knowledge transfer and implementation. I also hope to develop portable, possibly electronic, instruments that can be used to reach a wider, more global audience in this new flat world.

What is the greatest challenge facing the ACCP, and how will you address this challenge?

The greatest challenge to any organization in rapidly changing times is to avoid stagnation, remain innovative, and be nimble enough to adapt quickly to changes in the environment. With a rapidly evolving health-care system, unsustainable increases in health-care costs, increasingly restrictive regulations governing industry-society relationships, and increasing complexity in regulatory oversight of the practice of medicine,

"business as usual" will not address the needs of the modern cardiopulmonary and sleep caregiver.

The College is undertaking a major reorganization to position itself to address the changes required in our current environment. The infrastructure of the College is being realigned to improve internal coordination, linking functional units so that they can better respond to current and anticipated needs. The College's strategy for development of international relations has been better focused, targeting key regions with the largest demonstrated need and greatest potential benefit from ACCP partnership. We are building new educational and practice tools, including comprehensive simulation systems and quality improvement instruments that will broaden our educational reach both geographically and topically and that will enable practitioners to monitor and document personal performance and improve care quality, respectively.

Finally, I wish to codify the strategic continuum that has emerged under recent leadership. Instead of having the President articulate a distinct vision and direction each year, Dr Kay Guntupalli (President), Dr Suhail Raoof (President-Designate), and I (President-Elect) have developed a symbiotic relationship that allows implementation of a coordinated vision over a longer period of time. This allows us to move the College farther for the same amount of effort, providing a more consistent approach to new ideas and obstacles that might arise. These changes in how the College operates will improve support of our members in the care of their patients.

Finally, what is your charge to the members and new Fellows of ACCP?

I encourage all members, especially new Fellows, to *get involved*. By doing just that 15 years ago, I achieved the highest level of personal inspiration and professional rejuvenation in my career. If it can happen to an academic cardiologist and basic scientist like me, it can happen to you! Explore the College and its many facets. Find a path that stimulates your interest and get involved. You will not be disappointed, and you will not find a better professional home or a more welcoming family of professional colleagues and staff with whom to work. I guarantee it. ■

Dr Gutterman's primary research focus is on mechanisms regulating coronary vascular reactivity in the human heart. His work also includes translational studies examining the effect of exercise and diet on vascular endothelial function and the propensity for atherosclerosis. His laboratory has received continuous federal funding for over two decades, and he has authored more than 100 peer-reviewed scientific papers. Dr Gutterman has chaired NIH and AHA scientific study sections, is a member of the Association of University Cardiologists, and serves as an Associate Editor of the *American Journal of Physiology—Heart and Circulatory Physiology*.

We asked Dr Gutterman for some insights on his upcoming year as ACCP President.

What would you like to accomplish as President of the ACCP?

The ACCP has grown steadily over the past decade, substantially expanding its educational, practice support, and infrastructural components both in quantity and depth. This kind of growth requires careful organization

Continued from previous page

project, "Community Health Enrichment and Sustenance Training."
▶ The first annual Celebrating Our Diversity program, "Celebrating Our Diversity, India!" was presented by Anita Mathur, with assistance from other Ambassador members of her family.

2008-2009: Susan Mathers, Chair

- ▶ Under Susan's leadership, over 10,000 students worldwide had received the Lung LessonsSM tobacco education programs. Non-Ambassadors had started to ask for materials to present in their communities for the first time.
- ▶ Lung LessonsSM: A Presenter's Guide is now on YouTube.
- ▶ With the guidance of Mary Anne McCaffree, ACCP Ambassador and a trustee of the AMA, The CHEST Foundation signed a letter of agreement to collaborate with the AMA Alliance to promote Lung LessonsSM: A Presenter's Guide and to help increase the number of signatures on the AMA Alliance Screen Out petition.
- ▶ The Ambassadors Group notecards were offered for sale for the first time at

CHEST 2009 in San Diego. These colorful notecards were created from a selection of past winning poster contest designs.

- ▶ Dr Martin L. Bauer, FCCP, the 2009 Ambassadors Group Humanitarian Award recipient, presented his project, "Child Care and Conference for Parents Support Group of the Arkansas Center for Technology-Dependent Children in Little Rock, Arkansas." Dr Bauer described his work as the volunteer physician at Camp Aldersgate, a specially equipped camp for ventilator-dependent children.
- ▶ Marta Casaponsa de Morera presented "Celebrating Our Diversity: Spain."

2009-2010: Dr Jay Guntupalli, Chair

- ▶ The major focus of the Ambassadors Group continues to be the tobacco prevention education presentations in the schools, including the marketing of Lung LessonsSM: A Presenter's Guide that trains future presenters on key teaching points and available program materials through the Lending Library.
- ▶ The tobacco education programs in the schools locally and internationally have now reached over 12,000 students with tobacco prevention messages.

- ▶ The Handbook of Guiding Principles was amended to allow for an application process for Ambassadors Group chairs. To date, this has primarily been an honor provided to the spouse of the ACCP President.
- ▶ The Ambassadors set a goal to increase membership by 75 new Ambassadors by the end of the ACCP's 75th anniversary year.

2010-2011: Kathy Wilder will become Chair of the Ambassadors Group

- In addition to the major milestones noted above, the Ambassadors have been participating in the following:
- ▶ Annual Community Outreach Event programs in local schools during CHEST.
 - ▶ Membership drive and marketing activities.
 - ▶ Media outreach through articles in *CHEST Physician*.
 - ▶ Numerous social outings.
 - ▶ Membership directory.
 - ▶ An annual program on the following year's CHEST location.

As I was reviewing this Ambassadors Group timeline, I could not help but be amazed at the amount of work done in just a decade.

It's not just for women! Some of our male members include: Richard Irwin, Robert Johnson, Paul Kvale, Sidney Braman, Chase Johnson, Kotesch Rao, Bhimsen Rao, Sana Almassi, Jay Guntupalli, W. Michael Alberts, Michael Alberts, James Bisnet, Rainey Johnson, James Mathers, Sahir Raoof, Pascal Udekwo, and Peter Spiro.

It's not just for ACCP members! The Ambassadors Group is open to ACCP members' families and other committed individuals interested in furthering the goals of The CHEST Foundation, the philanthropic arm of the ACCP. Ambassador Group members participate in activities aimed at improving patient care and lung health at the local level.

It is impossible to mention, in this limited space, all of the dedicated people and their many activities with the Ambassadors Group—thank you to all of them!

Join the Ambassadors Group today! Go to www.chestfoundation.org/foundation/ambassadors/index.php for more information. ■

IPF: Two New Trials Actively Recruiting

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrosing lung disorder that affects over 120,000 Americans. To date, no FDA-approved drugs have been shown to reverse or halt the progression of this disease, which is often deadly. To address this problem, the National Institutes of Health established the IPF Clinical Research Network (IPFnet), which includes more than 20 centers across the United States charged with designing and conducting clinical trials in IPF. Recently, the network finished a clinical trial testing the use of sildenafil, a vasodilator, in patients with advanced IPF; the trial was published this year in the *New England Journal of Medicine* (*N Engl J Med.* 2010;363[7]:620).

The IPFnet is now engaged in two new clinical trials testing drugs that block pathways considered key for the development of tissue fibrosis. The first trial, termed PANTHER, will evaluate the effectiveness of antioxidants. An earlier study suggested a promising role for antioxidants in IPF, but too few patients were evaluated. PANTHER will also examine the role of steroids and related drugs. "Many patients are treated

with these types of drugs, yet we still don't know if steroids and antioxidants are effective. PANTHER will answer these questions once and for all, but only if patients enroll in this trial," said Dr Jesse Roman, Professor and Chair of the Department of Medicine at University of Louisville and chair of the IPFnet Education Committee.

The second trial being conducted by the IPFnet is called ACE. The ACE trial will explore the effectiveness of anti-coagulants in treating IPF based on published data suggesting a role for coagulation in lung fibrogenesis. ACE was designed to test the benefits of this intervention. "Well-designed clinical trials are being conducted in search of safe and effective treatments for IPF, but patient involvement in these trials is crucial for their success," said Dr Imre Noth, FCCP, Associate Professor at the University of Chicago and member of the IPFnet Executive Committee.

The new trials, PANTHER and ACE, are currently enrolling patients. To refer patients or to learn more about these trials, visit the IPFnet Web site (www.IPFnet.org) or contact the IPFnet site closest to your geographic location. ■

Attend the 12th Annual 'Making a Difference' Event

The CHEST Foundation will hold its annual Making a Difference Awards Ceremony and Presentation on Saturday, October 30, 2010. This year's dinner and awards presentation will be held in a room overlooking the bay. Included in the program will be the awarding of the 2010 D. Robert McCaffree, MD, Master FCCP Humanitarian Awards and the Industry Advisory Council Award. We anticipate it will be a lovely evening of celebration, recognition, and good cheer.

This is the 12th year that The Foundation will confer the D. Robert McCaffree, MD, Master FCCP Humanitarian Awards and the fourth year presenting the Ambassadors Group Humanitarian Award to deserving projects supported by ACCP members' expertise and volunteer time. These projects exemplify best practices of care and serve families worldwide who otherwise would be unable to access or afford medical care. The ACCP Industry Advisory Council will also present their annual monetary award to the Community Outreach Event partner, Laura Secord Elementary School.

The Making a Difference Awards Ceremony and Presentation will be held on Saturday, October 30, 2010, at the Vancouver Convention Centre, 1055 Canada Place, Third Floor, Rooms 301-305. The open reception will take place from 7:00 PM to 7:45 PM, with dinner and ceremonies following



from 8:00 PM to 10:30 PM. Invitations were mailed after Labor Day. Join your colleagues and friends for an evening of celebration and fun. Ticket price is \$150 per person (\$25 of ticket price is tax-deductible), and online registration is available

for those purchasing a ticket at www.chestfoundation.org. Making a Difference Society members at the \$1,000 level are eligible for two complimentary tickets, and annual donors at the \$500 level are eligible for one complimentary ticket, upon request. Contact Teri Ruiz at truiz@chestnet.org or (847) 498-8308 for more information.

The Awards Ceremony and Presentation sponsors, to date, are: Gilead Sciences Inc.; Merck & Co. Inc.; Genentech and Novartis; and Boehringer-Ingelheim Pharmaceuticals. ■

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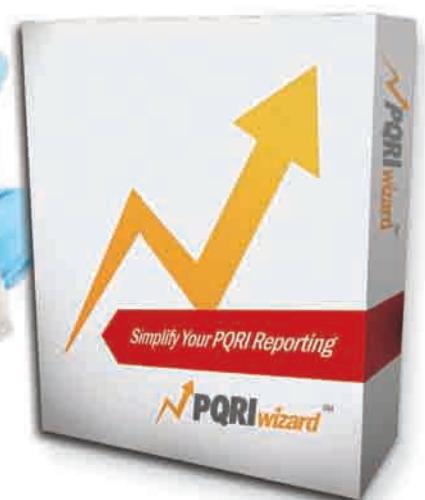
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SLEEP STRATEGIES

It is well-known that sleep plays a crucial role in quality of life, and sleep quality and sleep disorders are increasingly being studied in almost all populations of patients and disease states. However, there are little data in the medical literature regarding sleep in the palliative care setting. The ACCP's Sleep Institute and Palliative and End-of-Life Care Steering Committees have teamed up to review the medical literature and develop a consensus statement on sleep disorder evaluation and management in advanced life-threatening illness. Due to the lack of clinical trial data and the vast array of disease states and comorbidities that impact patients toward the end of life, this is a challenging but highly important and much-needed topic to address.

Symptoms predominantly associated with advanced life-threatening illnesses include anxiety, depression, pain, dyspnea, fatigue, and sleep disturbances. Some of these symptoms are related to the primary disease state and/or comorbidities; however, some can be side effects of therapies, including medications intended to improve quality of life. For example, benzodiazepines may relieve anxiety and help with insomnia, but in patients with sleep apnea or obstruction in the upper airway (eg, head and neck cancers), this may actually worsen breathing at night by increasing upper airway resistance during sleep, leading to sleep fragmentation and poorer sleep quality. Opioids, which are commonly used to treat pain at the end of life, can result in daytime hypersomnolence and, in some patients, may contribute to central sleep apnea and nocturnal hypoxemia.

Sleep disorders and sleep complaints are often underdiagnosed in patients with chronic illnesses. A retrospective review of patients admitted to a palliative care unit showed that patients self-reported an average of four symptoms, with pain being the most commonly reported at 72%. Bowel disturbance (32%), nausea/vomiting (30%), decreased mobility (30%), and decreased appetite (24%) were also highly prevalent. However, if questioned further in a systematic method, patients reported an average of eight more symptoms, with fatigue (56%), sleep problems (36%), and drowsiness (32%) being commonly prevalent symptoms (White. *J Palliat Med.* 2009;12[5]:447). This suggests that patients have a high prevalence of sleep-related problems

that may not be addressed unless specifically asked about by their physician. Another study using the validated Pittsburgh Sleep Quality Index questionnaire in advanced cancer patients on a palliative care ward suggested that 96% of the patients were "poor sleepers." Poor sleep was associated with worse scores on the Short Form 12 quality of life instrument and was also associated with higher scores of depression and hopelessness (Mystakidou et al. *Palliat Med.* 2009;23[1]:46).

Many studies regarding end-of-life and palliative care have been done in patients with advanced cancer.

Most of these have assessed measures of pain, fatigue, and dyspnea, with few randomized trials to

assess methods of controlling these symptoms. While there are increasingly more studies on sleep architecture and sleep-related breathing disorders in patients with chronic diseases, such as severe COPD or heart failure, these studies have not specifically addressed sleep issues in the palliative care setting.

A recent study by Gibbins and colleagues found that 47% of patients with advanced "incurable" cancer reported not sleeping well in spite of an average of 8.2 h of uninterrupted sleep per night. By actigraphy assessment, the sleep efficiency was indeed >90% but showed increased sleep fragmentation. Moreover, those patients with poorer sleep also had increased anxiety and pain (Gibbins et al. *J Pain Symptom Manage.* 2009;38[6]:860). The association with pain and sleep disruption is well known in the sleep literature. Perhaps improvement of sleep quality could influence pain management or control of mood disorders in advanced illnesses, as well.

Studies in patients with severe pulmonary diseases have objectively shown, through overnight polysomnograms, increased sleep fragmentation and increased "light sleep," also known as stage N1 or N2 sleep. It is widely known that sleep apnea is highly prevalent in patients with congestive heart failure, and use of nocturnal ventilation can improve sleep apnea and cardiac output in some of these patients. However, utilization of nocturnal ventilation for improving sleep quality for palliative purposes or quality of life in dying patients has not been addressed in a randomized, controlled trial.

There are few major papers from pulmonary organizations discussing palliative care in advanced life-threatening illness. One of these came from the ACCP Ethics Committee, chaired by Dr D. Robert McCaffree, Master FCCP, and was published in 2005 (Selecky et al. *Chest.* 2005;128[5]:3599). This statement on "Palliative and End-of-Life Care for Patients With Cardiopulmonary Diseases" eloquently addresses a comprehensive care recommendation plan

Sleep in Advanced Life-Threatening Illness

focused around patients with acute decompensating or chronically progressive cardiopulmonary diseases, suggesting that the patient's family should be an integral part of the care plan, in addition to a compassionate health-care provider who is knowledgeable in providing palliative care with a goal toward a multidisciplinary approach of care. The threefold plan for comprehensive care addresses support for the patient and family, care of the patient, and responsibilities of the physician or professional caregiver.

In March 2007, the American Thoracic Society Board of Directors adopted the ATS End-of-Life Care Task Force's "An Official American Thoracic Society Clinical Policy Statement: Palliative Care for Patients With Respiratory Diseases and Critical Illnesses" (*Am J*

Respir Crit Care Med. 2008;177[8]:912). This statement was a comprehensive, educational clinical guideline suggesting implementation of palliative care throughout the course of management in adult and pediatric patients with chronically progressive pulmonary disease. The statement does address the multidisciplinary approach with support for the family and recommendations for education of caregivers in palliative care, in addition to providing some detailed recommendations for treatment of dyspnea, pain, and withdrawal of life-sustaining therapies, in particular, mechanical ventilation.

The most recent paper released by the ACCP is the consensus statement regarding the management of dyspnea in patients with advanced cardiopulmonary disease (Mahler et al. *Chest.* 2010;137[3]:674).

While these papers are essential and informative, no article has specifically addressed issues regarding the prevalence or impact of sleep disturbances in progressive life-threatening illnesses or the appropriate recognition and treatment of sleep-related problems. The developing consensus statement will topics concerning insomnia, hypersomnia, circadian rhythm abnormalities, restless legs syndrome, pharmacotherapy in palliative care and its effects on sleep, sleep-related breathing disorders, and palliative use of nocturnal noninvasive positive pressure ventilation (NIPPV). These last topics broach controversial issues regarding when to use and discontinue NIPPV that is used for sleep apnea vs palliation of dyspnea. Data are limited, and standard consensus techniques are being used to assist with polling of experts in the field of sleep medicine and palliative care medicine on topics for which there is little clinical evidence.

In summary, sleep disorders are becoming increasingly more respected in the medical community as an important contributor to morbidity and mortality, and the impact of sleep disturbances on quality of life is well-known. In patients with advanced life-threatening illnesses, where the goal is to improve the quality and not quantity of life, it is only appropriate that the medical communities begin to recognize and treat this important aspect of their patients' health during their greatest time of need. ■

Dr Laura B. Herpel, FCCP
Assistant Professor of Medicine
Medical University of South Carolina
Division of Pulmonary, Critical Care,
Allergy & Sleep Medicine
Charleston, SC

Sleep Institute
American College
of Chest Physicians

Join the Ambassadors Group Today



Composed of ACCP members, their spouses, and friends, The CHEST Foundation's Ambassadors Group is actively recruiting members. Ambassadors Group members support the mission of The CHEST Foundation—to provide resources to advance the prevention and treatment of diseases of the chest—in a variety of ways, including:

- ▶ Educating elementary school students about the importance of lung health.
- ▶ Raising funds by selling the set of 12 colorful notecards using the past winning designs of children displaying the theme of "Love Your Lungs."
- ▶ Donating funds to support the annual Ambassadors Group Humanitarian Award.
- ▶ Participating on Ambassadors

Group Committees: Membership/Volunteer Appreciation, Hospitality, Poster Contest, or Marketing/Communications.

Ambassadors can join this active group in one of three membership categories: \$50 for US and Canada, \$35 for international, and \$10 for high-school and college youth. As an added benefit, those who join the Ambassadors Group by October 1, 2010, will have their guest fee waived for the CHEST 2010 meeting. Join The CHEST Foundation Ambassadors Group today at www.chestfoundation.org/foundation/ambassadors/membership.php.

Be sure to read the President's Report, with additional information about The CHEST Foundation's Ambassadors Group, in this issue on page 8. ■



Dr James Parish, FCCP
Section Editor,
Sleep Strategies

NETWORKS

Lung Cancer, Disclosures, Tobacco Use

Thoracic Oncology

Our NetWork has helped plan several key sessions for CHEST 2010 focusing on concepts important for the care of patients with thoracic malignancy. The CHEST 2010 program committee created an agenda with elements appealing to anyone with an interest in thoracic oncology. The first day of the meeting includes a session on proposed changes in the lung adenocarcinoma classification system.

CHEST 2010 will also take advantage of the international setting of this conference, including a session on Sunday, October 31, on the global impact of lung cancer. On Monday, the NetWork will highlight a session on the management of stage III lung cancer, where great controversy still exists and multidisciplinary involvement is most relevant. Tuesday includes the NetWork Open Meeting, where our highlighted speaker, Dr Annette McWilliams, will speak on early detection of lung cancer.

CHEST 2010 attendees can choose from additional highlights in the Thoracic Oncology curriculum, including Thoracic Oncology Literature Highlights and a session on long-term lung cancer survivors.

The NetWork also anticipates the

completion this year of the "ACCP Consensus Statement on the Classification of Autofluorescence Bronchoscopy Imaging and Pathologic Correlation for Preinvasive Squamous Cell Carcinoma of the Lung." An additional NetWork project in earlier stages deals with the management of the high-surgical-risk patient with early-stage lung cancer. This project will assemble the evidence on the treatment of "medically unresectable" early-stage lung cancer.

Dr Douglas Arenberg, FCCP
Vice-Chair

Members in Industry Maintaining Scientific Rigor in Scientific Disclosures and Presentations by Industry Physicians and Scientists

The debate over the granting of CME associated with scientific presentations by physicians and other health-care professionals and scientists employed by commercial interests has become an important component of the educational programs of medical associations and industry. As it evolves, some important facts about the internal review process required by most pharmaceutical and

medical device manufacturers should be known.

While a specific company can appear as a single undifferentiated organization, it is actually made up of differentiated units that can be broadly described as medical affairs, research and development, manufacturing, sales/marketing, and general administration. Physicians and other health-care professionals who work within the medical affairs unit may be organizationally separate from the other units. Such separation allows a muting of commercial influence and provides an opportunity for internal review by individuals removed from the authors. Most companies have a process in place for review of abstracts, manuscripts, and scientific presentations that must be completed before submission. This review is generally carried out by medical, legal, and/or regulatory management.

The internal review, akin to peer review, is conducted to assess the format and objectivity of the information being disclosed and to ensure that the disclosure fully addresses the issue or topic in a scientifically sound, balanced, and unbiased manner.

In addition to accurate content, the presentation or publication must comply with all federal regulations and fully disclose the authors' affiliation. The reviewers typically include colleagues with a medical or scientific background, a statistician, and legal and regulatory experts. Once passed by the internal review process, the manuscript or presentation must still survive external review by journal editors or meeting reviewers.

Industry-employed scientists strive to produce manuscripts and presentations that are free of commercial bias and can stand up to peer review and critique. They understand the need for accuracy and balance to maintain trust within the medical and research communities.

Assessing bias and the impact of potential or actual conflict of interest is a complex and evolving endeavor. Scientific disclosures by physicians and other health-care professionals employed by industry are under intense scrutiny. The internal review process used by most pharmaceutical and device companies is another layer of review to not only ensure quality but also to reduce and remove bias or commercial flavor to the disclosure.

Doug Schlichting, RN, MS, MPA
Steering Committee Member

Women's Health

Cigarette smoking during pregnancy leads to well-recognized adverse effects upon pregnancy and birth outcomes. However, prenatal tobacco exposure has also been associated with a variety of lasting effects on offspring, including behavioral effects, that are less widely

appreciated and that may have important implications for population health.

Numerous studies have looked at the link between prenatal tobacco smoke and ADHD among offspring. Pickett and colleagues tested the temperament of 18,819 9-month infants using the Carey Infant Temperament Scale. Those born to heavy smokers scored the poorest, a finding that persisted after adjustment for sociodemographic factors (Pickett et al. *J Epidemiol Community Health*. 2008;62[4]:318). This trend persisted in older offspring. In a cross-sectional study of 2,588 children ages 8-15 from the NHANES database, children whose mothers smoked prenatally were twice as likely to have ADHD compared with those not exposed (Froehlich et al. *Pediatrics*. 2009;124[6]:e1054).

Langley assessed 356 children ages 6-16 with ADHD and found that prenatal tobacco exposure was significantly associated with conduct disorder symptoms and a diagnosis of conduct disorder (Langley et al. *BMC Psychiatry*. 2007;7:26). In a population-based study of conduct problems in over 400 first-grade boys, Wakschlag and colleagues found an increased risk of oppositional defiant disorder among those exposed to

tobacco prenatally after controlling for confounders (OR=2.61) (Wakschlag et al. *J Am Acad Child Adolesc Psychiatry*. 2006;45[4]:461). In a prospective population study of 1,723 children, Höök and colleagues found an increased association between prenatal tobacco exposure and

externalizing, aggressive behavior and destructive behavior among children (Höök et al. *Acta Paediatr*. 2006;95[6]:671).

Maternal tobacco smoke has also been linked to increased substance abuse among offspring. In a 30-year prospective study, Buka and colleagues found that when adjusted for socioeconomic status and other confounders, offspring of mothers who smoked one pack per day or more had a twofold statistically significant increase in becoming nicotine-dependent themselves (Buka et al. *Am J Psychiatry*. 2003;160[11]:1978). Obesity rates are also higher among the offspring of smokers (Oken et al. *Int J Obes (Lond)*. 2008;32[2]:201), suggesting that some behavioral effects of in utero exposure may be mediated via general effects on neurotransmitter systems that mediate reward and satisfaction.

The adverse effects of antenatal tobacco exposure are more varied and far-reaching than broadly appreciated and represent an evolving area of research. The importance of efforts to reduce smoking among women of child-bearing age cannot be overemphasized.

Dr Rokhsara Rafii; and
Dr Susan Murin, MSc, FCCP

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Impact Factor Rises to 6.36

The impact factor of *CHEST* has risen to 6.36, according to the latest *Journal Citation Report*, an increase of over a full point since last year, placing *CHEST* among the top three journals in respiratory medicine. The impact factor measures the number of citations garnered by the

articles published in *CHEST*, but, more than that, it is a reflection of the high-quality work submitted by authors around the globe, the dedication of the peer reviewers, and the guidance of the Editorial Board and Editor in Chief, Dr Richard S. Irwin, Master FCCP. ■

'It Ain't Rocket Surgery'

Find information and musings about the intersection of technology and medicine on this fun and informative ACCP blog, written by ACCP Senior Vice President and *CHEST* Executive Editor, Stephen Welch (www.chestnet.org/accp/blogs/%20welch).

Steve says, "The title is a Yogi Berra-style mash-up of two sayings: it ain't rocket science and it ain't brain surgery. I hope the blog will be

educational, entertaining, and, occasionally, unconventional."

Recent topics have included augmented reality, iPad™ adoption by physicians, social media and medicine, and even tips on how to find hidden programs called "Easter eggs."

You can also receive related postings, links, and microblogs by following Steve on twitter at www.twitter.com/rocketsurgery99. ■

September Lessons



► Sleep-Disordered Breathing in Hospitalized Patients.

By Dr Natarajan Subramanian; and Dr W. McDowell Anderson, FCCP

► Steroid Resistance in Pulmonary Disease.

By Dr Donald Y. M. Leung; and Dr Daniel A. Searing

This Month in *CHEST*: Editor's Picks

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

► **Cigarette Smoking as a Cause of Cancers Other Than Lung Cancer: An Exploratory Study Using the Surveillance, Epidemiology, and End Results Program.** By Dr G. Ray et al.

► **Prevalence and Risk Factors of Habitual Snoring in Primary School Children.**

By Dr A. M. Li et al.

► **Adenosine Triphosphate Concentration of Exhaled Breath Condensate in Asthma.** By Dr Z. Lázár et al.



TOPICS IN PRACTICE MANAGEMENT

► **Electronic Medical Records: A Practitioner's Perspective on Evaluation and Implementation.** By Dr E. Diamond et al.

SELECTED REPORT

► **Hypersensitivity Pneumonitis Due to Molds in a Saxophone Player.** By Dr F. Metzger et al

CORRESPONDENCE

► **Trombone Player's Lung: A Probable New Cause of Hypersensitivity Pneumonitis.** By Dr M. L. Metersky et al.

INTERACTIVE PHYSIOLOGY GRAND ROUNDS (WITH ONLINE INTERACTIVE COMPONENT)

► **Respiratory Function in an Obese Patient With Sleep-Disordered Breathing.** By Dr A. H. Gifford et al.

POINT/COUNTERPOINT EDITORIALS

► **Adherence to Early Goal-Directed Therapy:**

Does It Really Matter?

Point: Yes. After a Decade, the Scientific Proof Speaks for Itself. By Dr E. P. Rivers.

► **Counterpoint: No. Both Risks and Benefits Require Further Study.** By Dr G. A. Schmidt.

► **Associated article: Factors Associated With Nonadherence to Early Goal-Directed Therapy in the ED.** By Dr M. E. Mikkelsen et al.

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- Best of Sleep Medicine: 2010 Review of the Literature
- Chest Radiology for the Pulmonologist
- Critical Care Ultrasonography
- Thromboembolic Disease and Pulmonary Hypertension



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Pulmonary, Critical Care, and Sleep Medicine physician needed to join growing group of four in employed position, just two hours from Chicago and St. Louis, in Bloomington, Illinois. OSF Saint Joseph Medical Center, a Level II Trauma Center, houses a state-of-the-art Comprehensive Care Unit of 32 beds, which includes both Critical Care and Step Down, a growing ambulatory pulmonary practice, sub-specialty clinics in pulmonary hypertension and lung nodules, and a six bed accredited sleep center. Come be a part of the OSF Healthcare, ranked # 1 in Integrated Healthcare Networks in Illinois. Call or send CV to: Rachel Reliford, Phone: 309-683-8352 or 800-232-3129 (8) Email: rachel.reliford@osfhealthcare.org Web: www.osfhealthcare.org

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A dynamic Pulmonary, Critical Care and Sleep group in one of the most rapidly growing suburbs of Phoenix Arizona seeks a fellowship trained associate. Partnership track available, exceptional benefits. J-1 visa OK. Patients are a healthy mixture of out and inpatients. Practice covers some prestigious hospitals in the area. Call 623-242-9830 or fax CV to 623-243-6733 or email: azlngsleep@yahoo.com

Pulmonary/ Critical Care

Exceptional opportunity to join a well established, private group including two pulmonologists, three hospitalists, two internal medicine physicians and several allied health professionals. Call would be 1:3. Group is offering a competitive salary and benefit package with early partnership track. The group's new medical office building is located adjacent to the hospital. Upper Valley Medical Center (UVMC) is a thriving state-of-the-art hospital located on a 130 acre campus conveniently located on I-75 minutes north of Dayton and within an hour's drive to Columbus and Cincinnati. Enjoy practicing at one hospital offering behavioral health services, dialysis center, long term care facilities, a four bed sleep lab, a Cancer Care Center, and much more! UVMC is affiliated with Premier Health Partners, a comprehensive health system serving southwest Ohio. Area communities offer excellent public and private schools, numerous parks, golf courses, two country clubs, cultural centers, indoor ice arena, nature preserves, and a vast array of housing options. For information contact: Wendy Castaldo, Director of Medical Staff Development, Upper Valley Medical Center, 1-800-772-3627 FAX: (937)440-8549, wcastaldo@uvmc.com (J-1 Visa waiver not available).

Connecticut

Option to join a well-established private group or be a hospital employee. Well-maintained facility with Hospitalist program. In and outpatient responsibilities. Area is known for historic homes and safe, friendly communities. Minutes to an International Airport and to Hartford. Susan Calame, Alpha Medical Group, 800.584.5001, scalame@alphamg.org Visit www.alphamg.org



WEST PENN ALLEGHENY HEALTH SYSTEM

Division Chief, Pulmonary Critical Care Medicine

West Penn Allegheny Health System is seeking a system Division Chief, Pulmonary Critical Care Medicine. West Penn Allegheny Health System is comprised of two tertiary and four community hospitals, serving Pittsburgh and the surrounding 5-state area. Combined, the hospitals have more than 2,200 beds, 11,000 employees, over 173,000 emergency visits and 80,000 patients admitted each year.

This position represents an excellent opportunity for a highly distinguished physician to provide leadership and direction for the Division of Pulmonary Critical Care Medicine for the West Penn Allegheny Health System. The System is comprised of Allegheny General Hospital, a 720-bed major academic medical center, Western Pennsylvania Hospital, a 524-bed comprehensive, tertiary care, regional teaching hospital and West Penn Hospital-Forbes Regional Campus, a 340-bed community hospital. In the Division of Pulmonary Critical Care Medicine, there are 44 physicians on staff, including 12 faculty members holding appointments from Temple University and Drexel University. Two hundred medical students rotate through the campuses yearly. In addition, there are 119 residents within the Department of Medicine and 9 fellows within the Division of Pulmonary Critical Care Medicine.

Candidates for this position must be board certified in Pulmonary Disease and/or Critical Care Medicine and eligible for a Pennsylvania license. The ideal candidate will have national and/or international recognition in his/her respective field as well as experience working in a multi-site academic medical center/health system.

To request addition information or to provide nominations, please contact:

Arnie Sherrin or Greg Gerson
c/o Alison Luckhurst
Korn/Ferry International
1835 Market Street, Suite 2000 - Philadelphia, PA 19103
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Department of Veterans Affairs Medical Center, Syracuse, New York seeks BC/BE Pulmonary/Critical Care physician with strong clinical, teaching and research skills. BC/BE in Sleep Medicine preferred. The position involves inpatient and outpatient Pulmonary Medicine, Critical Care Medicine and/or Sleep Medicine. The candidate will also have educational responsibilities for fellows, residents and medical students. The Medical Center offers state of the art equipment including endobronchial ultrasound capabilities. Candidates who will be finishing fellowship training or becoming board eligible in June 2011 will also be considered. Applicants must possess a license in any state and must qualify for an academic appointment at SUNY Upstate Medical University. The VA offers a competitive salary and a generous federal benefits package. Interested candidates should fax a cover letter referencing job number P08-10 and current curriculum vitae to: 315-425-2447, attention Linda Zavalas, Human Resources/05, VA Medical Center, 800 Irving Avenue, Syracuse, New York 13210; Email address: Linda.Zavalas@va.gov. Information on the VA Healthcare Network Upstate New York can be found at <http://www.syracuse.va.gov>. Position is subject to random drug testing. Equal Opportunity Employer.

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ACCP Joins Motion to Halt Red Flags Rule

The ACCP, in partnership with 26 other medical societies, has filed a motion to intervene as a plaintiff in the case of the *American Medical Association, the American Osteopathic Association, and the Medical Society for the District of Columbia v. Federal Trade Commission (FTC)* to declare unlawful and set aside the FTC's application of the Red Flags Rule to ACCP physician members as well as to physicians in general.

The Red Flags Rule would identify physicians as "creditors," requiring them to implement costly and time-consuming measures that could adversely impact patient care.

Read the ACCP's position on the Red Flags Rule at www.chestnet.org/accp/advocacy/priority-issues.

Watch for new electronic meeting planner tools that will enhance your ability to prepare for CHEST 2010: search sessions by keyword, build a daily itinerary, download session handouts, and even connect with other attendees using social media tools. Visit www.accpmeeting.org to get all the details about CHEST 2010 and more information about the

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TYGACIL® (tigecycline) Brief Summary

See package insert for full Prescribing Information. For further product information and current package insert, please visit www.pfizer.com or call our medical communications department toll-free at 1-800-934-5556.

INDICATIONS AND USAGE

TYGACIL is indicated for the treatment of adults with complicated skin and skin structure infections caused by *Escherichia coli*, *Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus agalactiae*, *Streptococcus anginosus* grp. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Streptococcus pyogenes*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, and *Bacteroides fragilis*.

TYGACIL is indicated for the treatment of adults with complicated intra-abdominal infections caused by *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus anginosus* grp. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Clostridium perfringens*, and *Peptostreptococcus micros*.

TYGACIL is indicated for the treatment of adults with community-acquired pneumonia infections caused by *Streptococcus pneumoniae* (penicillin-susceptible isolates), including cases with concurrent bacteremia, *Haemophilus influenzae* (beta-lactamase negative isolates), and *Legionella pneumophila*.

CONTRAINDICATIONS

TYGACIL is contraindicated for use in patients who have known hypersensitivity to tigecycline.

WARNINGS AND PRECAUTIONS

Anaphylaxis/Anaphylactoid Reactions

Anaphylaxis/anaphylactoid reactions have been reported with nearly all antibacterial agents, including TYGACIL, and may be life-threatening. TYGACIL is structurally similar to tetracycline-class antibiotics and should be administered with caution in patients with known hypersensitivity to tetracycline-class antibiotics.

Hepatic Effects

Increases in total bilirubin concentration, prothrombin time and transaminases have been seen in patients treated with tigecycline. Isolated cases of significant hepatic dysfunction and hepatic failure have been reported in patients being treated with tigecycline. Some of these patients were receiving multiple concomitant medications. Patients who develop abnormal liver function tests during tigecycline therapy should be monitored for evidence of worsening hepatic function and evaluated for risk/benefit of continuing tigecycline therapy. Adverse events may occur after the drug has been discontinued.

Mortality Imbalance and Lower Cure Rates in Ventilator-Associated Pneumonia

A study of patients with hospital acquired pneumonia failed to demonstrate the efficacy of TYGACIL. In this study, patients were randomized to receive TYGACIL (100 mg initially, then 50 mg every 12 hours) or a comparator. In addition, patients were allowed to receive specified adjunctive therapies. The sub-group of patients with ventilator-associated pneumonia who received TYGACIL had lower cure rates (47.9% versus 70.1% for the clinically evaluable population) and greater mortality (25/131 [19.1%] versus 14/122 [11.5%]) than the comparator.

Use During Pregnancy

TYGACIL may cause fetal harm when administered to a pregnant woman. If the patient becomes pregnant while taking tigecycline, the patient should be apprised of the potential hazard to the fetus. Results of animal studies indicate that tigecycline crosses the placenta and is found in fetal tissues. Decreased fetal weights in rats and rabbits (with associated delays in ossification) and fetal loss in rabbits have been observed with tigecycline [see **USE IN SPECIFIC POPULATIONS**].

Tooth Development

The use of TYGACIL during tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). Results of studies in rats with TYGACIL have shown bone discoloration. TYGACIL should not be used during tooth development unless other drugs are not likely to be effective or are contraindicated.

Clostridium difficile-Associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including TYGACIL, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*. *C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxic 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.

Patients With Intestinal Perforation

Caution should be exercised when considering TYGACIL monotherapy in patients with complicated intra-abdominal infections (cIAI) secondary to clinically apparent intestinal perforation. In cIAI studies (n=1642), 6 patients treated with TYGACIL and 2 patients treated with imipenem/cilastatin presented with intestinal perforations and developed sepsis/septic shock. The 6 patients treated with TYGACIL had higher APACHE II scores (median = 13) versus the 2 patients treated with imipenem/cilastatin (APACHE II scores = 4 and 6). Due to differences in baseline APACHE II scores between treatment groups and small overall numbers, the relationship of this outcome to treatment cannot be established.

Tetracycline-Class Effects

TYGACIL is structurally similar to tetracycline-class antibiotics and may have similar adverse effects. Such effects may include: photosensitivity, pseudotumor cerebri, and anti-anabolic action (which has led to increased BUN, azotemia, acidosis, and hyperphosphatemia). As with tetracyclines, pancreatitis has been reported with the use of TYGACIL.

Superinfection

As with other antibacterial drugs, use of TYGACIL may result in overgrowth of non-susceptible organisms, including fungi. Patients should be carefully monitored during therapy. If superinfection occurs, appropriate measures should be taken.

Development of Drug-Resistant Bacteria

Prescribing TYGACIL 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.

ADVERSE REACTIONS

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

In clinical trials, 2514 patients were treated with TYGACIL. TYGACIL was discontinued due to adverse reactions in 7% of patients compared to 6% for all comparators. Table 1 shows the incidence of treatment-emergent adverse reactions through test of cure reported in ≥2% of patients in these trials.

Table 1. Incidence (%) of Adverse Reactions Through Test of Cure Reported in ≥2% of Patients Treated in Clinical Studies

Body System Adverse Reactions	TYGACIL (N=2514)	Comparators ^a (N=2307)
Body as a Whole		
Abdominal pain	6	4
Abscess	3	3
Asthenia	3	2
Headache	6	6
Infection	8	7
Cardiovascular System		
Phlebitis	3	4
Digestive System		
Diarrhea	12	11
Dyspepsia	2	2
Nausea	26	13
Vomiting	18	9
Hemic and Lymphatic System		
Anemia	4	4
Metabolic and Nutritional		
Alkaline Phosphatase Increased	4	3
Amylase Increased	3	2
Bilirubinemia	2	1
BUN Increased	3	1
Healing Abnormal	4	3
Hypoproteinemia	5	3
SGOT Increased ^b	4	5
SGPT Increased ^b	5	5
Nervous System		
Dizziness	3	3
Skin and Appendages		
Rash	3	4

^a Vancomycin/Aztreonam, Imipenem/Cilastatin, Levofloxacin, Linezolid.

^b LFT abnormalities in TYGACIL-treated patients were reported more frequently in the post therapy period than those in comparator-treated patients, which occurred more often on therapy.

In all Phase 3 and 4 studies that included a comparator, death occurred in 3.9% (147/3788) of patients receiving TYGACIL and 2.9% (105/3646) of patients receiving comparator drugs. An increase in all-cause mortality has been observed across phase 3 and 4 clinical studies in TYGACIL treated patients versus comparator. The cause of this increase has not been established. This increase should be considered when selecting among treatment options. (See Table 2.)

Table 2. Patients with Adverse Events with Outcome of Death by Infection Type

Infection Type	n/N	TYGACIL %	n/N	Comparator %	Risk Difference* % (95% CI)
Approved Indications					
cSSSI	12/834	1.4	6/813	0.7	0.7 (-0.5, 1.9)
cIAI	40/1382	2.9	27/1393	1.9	1.0 (-0.3, 2.2)
CAP	12/424	2.8	11/422	2.6	0.2 (-2.3, 2.7)
Combined	64/2640	2.4	44/2628	1.7	0.7 (-0.0, 1.6)
Unapproved Indications					
HAP	65/467	13.9	56/467	12.0	1.9 (-2.6, 6.4)
Non-VAP ^b	40/336	11.9	42/345	12.2	-0.3 (-5.4, 4.9)
VAP ^b	25/131	19.1	14/122	11.5	7.6 (-2.0, 16.9)
RP	11/128	8.6	2/43	4.7	3.9 (-9.1, 11.6)
DFI	7/553	1.3	3/508	0.6	0.7 (-0.8, 2.2)
Combined	84/1148	7.2	61/1018	6.0	1.2 (-1.0, 3.4)

CAP = Community-acquired pneumonia; cIAI = Complicated intra-abdominal infections; cSSSI = Complicated skin and skin structure infections; HAP = Hospital-acquired pneumonia; VAP = Ventilator-associated pneumonia; RP = Resistant pathogens; DFI = Diabetic foot infections.

* The difference between the percentage of patients who died in TYGACIL and comparator treatment groups.

^b These are subgroups of the HAP population.

Note: The studies include 300, 305, 900 (cSSSI), 301, 306, 315, 316, 400 (cIAI), 308 and 313 (CAP), 311 (HAP), 307 [Resistant gram-positive pathogen study in patients with MRSA or Vancomycin-Resistant Enterococcus (VRE)], and 319 (DFI with and without osteomyelitis).

In comparative clinical studies, infection-related serious adverse events were more frequently reported for subjects treated with TYGACIL (7%) versus comparators (6%). Serious adverse events of sepsis/septic shock were more frequently reported for subjects treated with TYGACIL (2%) versus comparators (1%). Due to baseline differences between treatment groups in this subset of patients, the relationship of this outcome to treatment cannot be established [see **WARNINGS AND PRECAUTIONS**].

The most common treatment-emergent adverse reactions were nausea and vomiting which generally occurred during the first 1–2 days of therapy. The majority of cases of nausea and vomiting associated with TYGACIL and comparators were either mild or moderate in severity. In patients treated with TYGACIL, nausea incidence was 26% (17% mild, 8% moderate, 1% severe) and vomiting incidence was 18% (11% mild, 6% moderate, 1% severe).

In patients treated for complicated skin and skin structure infections (cSSSI), nausea incidence was 35% for TYGACIL and 9% for vancomycin/aztreonam; vomiting incidence was 20% for TYGACIL and 4% for vancomycin/aztreonam. In patients treated for complicated intra-abdominal infections (cIAI), nausea incidence was 25% for TYGACIL and 21% for imipenem/cilastatin; vomiting incidence was 20% for TYGACIL and 15% for imipenem/cilastatin. In patients treated for community-acquired bacterial pneumonia (CAP), nausea incidence was 24% for TYGACIL and 8% for levofloxacin; vomiting incidence was 16% for TYGACIL and 6% for levofloxacin.

Discontinuation from tigecycline was most frequently associated with nausea (1%) and vomiting (1%).

For comparators, discontinuation was most frequently associated with nausea (<1%).

The following adverse reactions were reported infrequently (<2%) in patients receiving TYGACIL in clinical studies: *Body as a Whole*: injection site inflammation, injection site pain, injection site reaction, septic shock, allergic reaction, chills, injection site edema, injection site phlebitis

Cardiovascular System: thrombophlebitis

Digestive System: anorexia, jaundice, abnormal stools

Metabolic/Nutritional System: increased creatinine, hypocalcemia, hypoglycemia, hyponatremia

Special Senses: taste perversion

Hemic and Lymphatic System: partial thromboplastin time (aPTT), prolonged prothrombin time (PT), eosinophilia, increased international normalized ratio (INR), thrombocytopenia

Skin and Appendages: pruritus

Urogenital System: vaginal moniliasis, vaginitis, leukorrhea

Post-Marketing Experience

The following adverse reactions have been identified during postapproval use of TYGACIL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish causal relationship to drug exposure. Anaphylaxis/anaphylactoid reactions, acute pancreatitis, hepatic cholestasis, and jaundice.

DRUG INTERACTIONS

Warfarin

Prothrombin time or other suitable anticoagulation test should be monitored if tigecycline is administered with warfarin [see **CLINICAL PHARMACOLOGY (12.3)** in full Prescribing Information].

Oral Contraceptives

Concurrent use of antibacterial drugs with oral contraceptives may render oral contraceptives less effective.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects—Pregnancy Category D [see **WARNINGS AND PRECAUTIONS**]

Tigecycline was not teratogenic in the rat or rabbit. In preclinical safety studies, ¹⁴C-labeled tigecycline crossed the placenta and was found in fetal tissues, including fetal bone structures. The administration of tigecycline was associated with slight reductions in fetal weights and an increased incidence of minor skeletal anomalies (delays in bone ossification) at exposures of 5 times and 1 times the human daily dose based on AUC in rats and rabbits, respectively (28 mcg·hr/mL and 6 mcg·hr/mL at 12 and 4 mg/kg/day). An increased incidence of fetal loss was observed at maternotocidal doses in the rabbits with exposure equivalent to human dose.

There are no adequate and well-controlled studies of tigecycline in pregnant women. TYGACIL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Results from animal studies using ¹⁴C-labeled tigecycline indicate that tigecycline is excreted readily via the milk of lactating rats. Consistent with the limited oral bioavailability of tigecycline, there is little or no systemic exposure to tigecycline in nursing pups as a result of exposure via maternal milk.

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 TYGACIL is administered to a nursing woman [see **WARNINGS AND PRECAUTIONS**].

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 years have not been established. Because of effects on tooth development, use in patients under 8 years of age is not recommended [see **WARNINGS AND PRECAUTIONS**].

Geriatric Use

Of the total number of subjects who received TYGACIL in Phase 3 clinical studies (n=2514), 664 were 65 and over, while 288 were 75 and over. No unexpected overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity to adverse events of some older individuals cannot be ruled out.

No significant difference in tigecycline exposure was observed between healthy elderly subjects and younger subjects following a single 100 mg dose of tigecycline [see **CLINICAL PHARMACOLOGY (12.3)** in full Prescribing Information].

Hepatic Impairment

No dosage adjustment is warranted in patients with mild to moderate hepatic impairment (Child Pugh A and Child Pugh B). In patients with severe hepatic impairment (Child Pugh C), the initial dose of tigecycline should be 100 mg followed by a reduced maintenance dose of 25 mg every 12 hours. Patients with severe hepatic impairment (Child Pugh C) should be treated with caution and monitored for treatment response [see **CLINICAL PHARMACOLOGY (12.3)** and **DOSE AND ADMINISTRATION (2.2)** in full Prescribing Information].

OVERDOSAGE

No specific information is available on the treatment of overdose with tigecycline. Intravenous administration of TYGACIL at a single dose of 300 mg over 60 minutes in healthy volunteers resulted in an increased incidence of nausea and vomiting. In single-dose intravenous toxicity studies conducted with tigecycline in mice, the estimated median lethal dose (LD₅₀) was 124 mg/kg in males and 98 mg/kg in females. In rats, the estimated LD₅₀ was 106 mg/kg for both sexes. Tigecycline is not removed in significant quantities by hemodialysis.

This Brief Summary is based on TYGACIL direction circular W10521C013 ET01, revised 09/09.



Expanded broad-spectrum coverage^{3*} is on your side

Gram positives
Gram negatives
Atypical
Anaerobes

*TYGACIL does not cover *Pseudomonas aeruginosa*.

TYGACIL is indicated for the treatment of adults with:

- **Complicated skin and skin structure infections** caused by *Escherichia coli*, *Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus agalactiae*, *Streptococcus anginosus* grp. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Streptococcus pyogenes*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, and *Bacteroides fragilis*
- **Complicated intra-abdominal infections** caused by *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus anginosus* grp. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Clostridium perfringens*, and *Peptostreptococcus micros*
- **Community-acquired bacterial pneumonia** caused by *Streptococcus pneumoniae* (penicillin-susceptible isolates), including cases with concurrent bacteremia, *Haemophilus influenzae* (beta-lactamase negative isolates), and *Legionella pneumophila*

Important Safety Information

- TYGACIL is contraindicated in patients with known hypersensitivity to tigecycline
- Anaphylaxis/anaphylactoid reactions have been reported with nearly all antibacterial agents, including tigecycline, and may be life-threatening. TYGACIL should be administered with caution in patients with known hypersensitivity to tetracycline-class antibiotics
- Isolated cases of significant hepatic dysfunction and hepatic failure have been reported in patients being treated with tigecycline. Some of these patients were receiving multiple concomitant medications. Patients who develop abnormal liver function tests during tigecycline therapy should be monitored for evidence of worsening hepatic function. Adverse events may occur after the drug has been discontinued
- The safety and efficacy of TYGACIL in patients with hospital-acquired pneumonia have not been established
- **An increase in all-cause mortality has been observed across phase 3 and 4 clinical studies in TYGACIL-treated patients versus comparator-treated patients. The cause of this increase has not been established. This increase in all-cause mortality should be considered when selecting among treatment options**
- **TYGACIL may cause fetal harm when administered to a pregnant woman**
- **The use of TYGACIL during tooth development may cause permanent discoloration of the teeth.** TYGACIL should not be used during tooth development unless other drugs are not likely to be effective or are contraindicated
- Acute pancreatitis, including fatal cases, has occurred in association with tigecycline treatment. Consideration should be given to the cessation of the treatment with tigecycline in cases suspected of having developed pancreatitis
- *Clostridium difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including TYGACIL, and may range in severity from mild diarrhea to fatal colitis
- Monotherapy should be used with caution in patients with clinically apparent intestinal perforation
- TYGACIL is structurally similar to tetracycline-class antibiotics and may have similar adverse effects. Such effects may include: photosensitivity, pseudotumor cerebri, and anti-anabolic action (which has led to increased BUN, azotemia, acidosis, and hyperphosphatemia). As with tetracyclines, pancreatitis has been reported with the use of TYGACIL
- To reduce the development of drug-resistant bacteria and maintain the effectiveness of TYGACIL and other antibacterial drugs, TYGACIL should be used only to treat infections proven or strongly suspected to be caused by susceptible bacteria. As with other antibacterial drugs, use of TYGACIL may result in overgrowth of non-susceptible organisms, including fungi
- The most common adverse reactions (incidence >5%) are nausea, vomiting, diarrhea, abdominal pain, headache, and increased SGPT
- Prothrombin time or other suitable anticoagulant test should be monitored if TYGACIL is administered with warfarin
- Concurrent use of antibacterial drugs with oral contraceptives may render oral contraceptives less effective
- The safety and effectiveness of TYGACIL in patients below age 18 and lactating women have not been established

Please see brief summary of Prescribing Information on adjacent page.

References: 1. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Clin Infect Dis.* 2010;50:133-164. 2. May AK, Stafford RE, Bulger EM, et al. Treatment of complicated skin and soft tissue infections. *Surg Infect.* 2009;10:467-499. 3. TYGACIL® (tigecycline) Prescribing Information, Wyeth Pharmaceuticals Inc.