Drug Resistance Triggers Lung Ca Transformation

Adenocarcinoma shifted to SCLC.

BY PATRICE WENDLING
Elsevier Global Medical News

CHICAGO – A small study provides compelling data that both the genotype and phenotype of non-small cell lung cancers can transform as part of acquired resistance to tyrosine kinase inhibitors.

Repeat tumor biopsies revealed that the histologic diagnosis of the tumor shifted from adenocarcinoma to small cell lung cancer (SCLC) in 14% of 37 consecutive patients with epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer (NSCLC) and acquired tyrosine kinase inhibitor (TKI) resistance, Dr. Lecia Sequist said during the plenary session at the Chicago Multidisciplinary Symposium in Thoracic Oncology.

The original L858R mutation or E 19 deletion was retained in all cases but, in one patient, an additional PIK3CA mutation was seen only when the tumor shifted to SCLC.

Although other groups have documented sporadic case reports of transformation, Dr. Sequist called the 14% transformation rate remarkable. “I think this points to a broader conceptual model of acquired resistance, and we need to think very carefully about doing more repeat biopsies in patients,” she said.

EGFR-mutant NSCLC is highly sensitive to EGFR TKI therapy, but acquired resistance develops at about 9-12 months due to T790M mutations in half of patients and MET amplification in 10-15%. Elucidating the remaining mechanisms of drug resistance is of great clinical and scientific significance, said Dr. Sequist of Massachusetts General Hospital Cancer Center, Boston.

See Drug Resistance • page 8

Passive Smoking Increases BP in Kids

BY SHARON WORCESTER
Elsevier Global Medical News

Parental smoking was an independent risk factor for elevated systolic blood pressure in 4,236 preschool children who were part of a blood pressure screening project in Germany.

Current cigarette smoking was reported by 29% of fathers and 21% of mothers of the children in the study, and both parents reported smoking in 12% of cases. Children who had a parent who smoked were significantly more likely to have higher systolic blood pressure, even after adjusting for risk factors such as body mass index, parental hypertension, and birth weight.

Giacomo D. Simonetti of the University of Heidelberg (Germany), and his colleagues reported.

Having a parent who was a smoker increased the likelihood of having a systolic blood pressure in the top 15% of the population by 21%, the investigators found (Circulation 2010;122:2859).

See Smoking • page 23

Thinking about a change? Interested in relocating? Go where the jobs are ...
News From the College

15
Critical Care Commentary

The choice of treatment for the management of adult pulmonary fungal infections should be based on diagnostic findings and individual risk factors, according to a new policy statement issued by the American Thoracic Society. In most cases, treatment of fungal infections must be based on the causative fungus, the severity of disease, and the clinical features of each patient,” the authors wrote.

The policy statement provides organism- and infection-site specific guidelines for therapy, including dosing recommendations, and incorporates the range of novel antifungal medications, such as the triazoles, echinocandins, and echinocandins, that have been introduced since the previous guidelines were published in 1988, according to Dr. Andrew Limper, FCP, of the Mayo Clinic in Rochester, Minn., and his colleagues on the American Thoracic Society’s Fungal Infections Working Group. In particular, the recommendations outline the management of endemic mycoses, including histoplasmosis, sporotrichosis, blastomycosis, and coccidioidomycosis; fungal infections with increased prevalence in immune-compromised and critically ill patients, including cryptococcosis, aspergillosis, candidiasis, and Pneumocystis pneumonia; and rare and emerging fungal infections, such as zygomycoses, halosporinomyces, the phaeohyphomycoses, and infections related to Trichosporon species (Am. J. Respir. Crit. Care. Med. 2011; 183:96-128).

Endemic Mycoses

The guidelines recommend treatment with itraconazole for mild to moderate histoplasmosis, sporotrichosis, and blastomycosis, and treatment with amphotericin B for severe disease (followed by itraconazole in patients with sporotrichosis).

Patients with severe histoplasmosis with diffuse pulmonary infiltrates and critically ill patients with severe pulmonary blastomycosis may require systemic therapy, as well. Further, for patients with pulmonary blastomycosis and concomitant CNS involvement, the guidelines recommend trimethoprim and sulfamethoxazole, liposomal amphotericin B (vs. amphotericin B deoxycholate) and fluconazole “should be considered due to theoretic but better CNS penetration,” the authors of the guidelines wrote.

Antifungal therapy is not recommended for primary pulmonary coccidiodiomycosis in immunocompetent patients who have no risk factors for dissemination, while patients with disseminated infection should be treated with an extended-spectrum triazole, according to the guidelines, which also specify that critically ill patients with disseminated paracoccidioidomycosis should be treated initially with amphotericin B, followed by ketoconazole, itraconazole, or sulfadiazine.

Immunocompromised Patients

The treatment options for fungal infections in patients with compromised immune systems, including transplant patients, those being treated for autoimmune inflammatory conditions, and HIV-infected patients, include oral trimethoprim and sulfamethoxazole, oral pramiquat plus clindamycin, and rapidly control the underlying illness. The majority of affected patients are immunocompromised,” the guidelines wrote. “A primary strategy for management of these infections with underlying diseases is to maximize immunosuppressive drugs, provide immunostimulants, and/or rapidly control the underlying diseases or conditions, such as HIV infection, diabetes, and/or chemotherapy-induced neutropenia,” they stated.

The third management strategy includes specific antifungal recommendations, which may be supported by empirical and clinical studies, and includes species-specific antifungal recommendations, such as amphotericin B for zygomycosis, voriconazole or posaconazole, and may be used in combination with antifungal therapy for invasive pulmonary aspergillosis, voriconazole or itraconazole for mild to moderate chronic necrotizing aspergillosis, and liposomal amphotericin B or intravenous voriconazole for severe chronic necrotizing aspergillosis.

The authors reported financial relationships with AlphaMed Pharmaceuticals, Pfizer, Ortho-McNeil, Mirabella Technologies, AstraZeneca, SmithKline, Bayer, Novartis, Aradigm, Astellas, Enzon, Merck, and Schering-Plough.

CHEST PHYSICIAN

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The TRIAZOLES AND ECHINOCANDINS HAVE BEEN INTRODUCED SINCE THE PREVIOUS GUIDELINES WERE PUBLISHED IN 1988.

The exact dosing and duration of treatment for these emerging, rare infections are not precise, and consultation with an expert in infectious disease
Indication
REVATIO is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability and delay clinical worsening. Delay in clinical worsening was demonstrated when REVATIO was added to background epoprostenol therapy. The efficacy of REVATIO has not been adequately evaluated in patients taking bosentan concurrently.

Important Safety Information
Do not use REVATIO in patients taking organic nitrates in any form, either regularly or intermittently. Consistent with its known effects on the nitric oxide/cGMP pathway, sildenafil was shown to potentiate the hypotensive effects of nitrates.

Before starting REVATIO, physicians should carefully consider whether their patients with underlying conditions could be adversely affected by the mild and transient vasodilatory effects of REVATIO on blood pressure. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD) and administration of REVATIO to these patients is not recommended. Should signs of pulmonary edema occur when sildenafil is administered, the possibility of associated PVOD should be considered.

Caution is advised when PDE5 inhibitors, such as REVATIO, are administered with α-blockers as both are vasodilators with blood pressure lowering effects.

In PAH patients, the concomitant use of vitamin K antagonists and REVATIO resulted in a greater incidence of reports of bleeding (primarily epistaxis) versus placebo. The incidence of epistaxis was higher in patients with PAH secondary to CTD (sildenafil 13%, placebo 0%) than in PPH patients (sildenafil 3%, placebo 2%).

Co-administration of REVATIO with potent CYP3A4 inhibitors, eg, ketoconazole, itraconazole, and ritonavir, is not recommended as serum concentrations of sildenafil substantially increase. Co-administration of REVATIO with CYP3A4 inducers, including bosentan; and more potent inducers such as barbiturates, carbamazepine, phenytoin, efavirenz, nevirapine, rifampin, and rifabutin, may alter plasma levels of either or both medications. Dosage adjustment may be necessary.

Non-arteritic anterior ischemic optic neuropathy (NAION) has been reported post-marketing in temporal association with the use of PDE5 inhibitors for the treatment of erectile dysfunction, including sildenafil. It is not possible to determine if these events are related to PDE5 inhibitors or to other factors. Physicians should advise patients to seek immediate medical attention in the event of sudden loss of vision while taking PDE5 inhibitors, including REVATIO.

Sudden decrease or loss of hearing has been reported in temporal association with the intake of PDE5 inhibitors, including REVATIO. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE5 inhibitors, including REVATIO.

REVATIO should be used with caution in patients with anatomical deformation of the penis or patients who have conditions which may predispose them to priapism. REVATIO contains sildenafil, the same active ingredient found in VIAGRA®. Combinations of REVATIO with VIAGRA® or other PDE5 inhibitors have not been studied. Patients taking REVATIO should not take VIAGRA® or other PDE5 inhibitors.

Patients with the following characteristics did not participate in the preapproval clinical trial: patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months, unstable angina, hypertension (BP >170/110), retinitis pigmentosa, or patients on bosentan. The safety of REVATIO is unknown in patients with bleeding disorders and patients with active peptic ulceration. In these patients, physicians should prescribe REVATIO with caution.

The most common side effects of REVATIO (placebo-subtracted) were epistaxis (8%), headache (7%), dyspepsia (6%), flushing (6%), and insomnia (6%). Adverse events of REVATIO injection were similar to those seen with oral tablets.

The most common side effects of REVATIO (placebo-subtracted) as an adjunct to intravenous epoprostenol were headache (23%), edema (14%), dyspepsia (14%), pain in extremity (11%), diarrhea (7%), nausea (7%), and nasal congestion (7%).

Please see Brief Summary of Prescribing Information on the following pages.
COPD in Acute MI Patients Spells Trouble

CHICAGO – Chronic obstructive pulmonary disease is a powerful risk factor for in-hospital mortality or cardiogenic shock in patients with ST-elevation MI, a large retrospective study showed.

The clinical inference is that the reduced cardiopulmonary reserve imposed by COPD – a disease often marked by pulmonary hypertension and right ventricular dysfunction – renders the circulatory system less capable of coping with the effects of an MI, Dr. Kohki Wakabayashi said at the annual scientific sessions of the American Heart Association.

Of 3,249 patients who underwent emergent percutaneous coronary intervention for STEMI at Washington (D.C.) Hospital Center, 365 had COPD. Their rate of in-hospital mortality or cardiogenic shock (24%) was substantially greater than in patients with no COPD (14%). Patients with COPD were significantly older, were more often smokers and women, and had a higher prevalence of chronic renal insufficiency, hypertension, and diabetes. In a multivariate log regression analysis adjusted for these factors, COPD emerged as the single strongest independent predictor of in-hospital mortality or cardiogenic shock in patients undergoing PCI for STEMI, with an associated 83% increased risk, said Dr. Wakabayashi of the center.

REVATIO® (SILDENAFIL)

Brief Summary of Prescribing Information

INDICATIONS AND USAGE: REVATIO® is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise ability and delay clinical worsening. The delay in clinical worsening was demonstrated when REVATIO was added to background epoprostenol therapy.

Limitation of Use

The efficacy of REVATIO has not been adequately evaluated in patients taking bosentan concurrently.

DOSEAGE AND ADMINISTRATION

Pulmonary Arterial Hypertension (PAH)

REVATIO Tablets

The recommended dose of REVATIO is 20 mg three times a day (TID). REVATIO tablets should be taken approximately 4-6 hours apart, with or without food.

In the clinical trial no greater efficacy was achieved with the use of higher doses. Treatment with doses higher than 20 mg TID is not recommended. Dosages lower than 20 mg TID were not tested. Whether dosages lower than 20 mg TID are effective is not known.

REVATIO Injection

REVATIO injection is for the continued treatment of patients with pulmonary arterial hypertension (PAH) who are currently prescribed oral REVATIO and who are temporarily unable to take oral medication.

The recommended dose is 10 mg (corresponding to 12.5 mL) administered as an intravenous bolus injection three times a day. The dose of REVATIO injection does not need to be adjusted for body weight.

A 10 mg dose of REVATIO injection is predicted to provide pharmacological effect of sildenafil and its bio-activated metabolite equivalent to that of a 20 mg oral dose.

CONTRAINdications

Use with Organic Nitrates

Do not use REVATIO in patients taking organic nitrates in any form, either regularly or intermittently. Consistent with known effects on the nitric oxide/cGMP pathway, sildenafil is known to potentiate the hypotensive effects of nitrates.

Hypersensitivity Reactions

REVATIO is contraindicated in patients with a known hypersensitivity to sildenafil or any component of the tablet.

Rare cases of hypersensitivity have been reported in association with the use of sildenafil including anaphylactic reactions and anaphylactic shock. The majority of reported events were non-serious hypersensitivity reactions.

WARNINGS AND PREcautions

Cardiovascular Effects

REVATIO has vasodilatory properties, resulting in mild and transient decreases in blood pressure. Before prescribing REVATIO, carefully consider whether patients with certain underlying conditions could be adversely affected by such vasodilatory effects (e.g., patients with hypotension [BP < 90/50 mm Hg], decompensated heart failure, severe left ventricular outflow obstruction, or autonomic dysfunction).

Pulmonary vasodilators may worsen the pulmonary status of patients with pulmonary veno-occlusive disease (PVOD). There are no clinical data on the administration of REVATIO to patients with veno-occlusive disease, administration of REVATIO to such patients is not recommended. Should signs of pulmonary edema occur when REVATIO is administered, consider the possibility of associated PVOD.

As there are no randomized clinical data on the safety or efficacy of REVATIO in the following groups, prescribe with caution:

• Patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months;
• Patients with coronary artery disease causing unstable angina;
• Patients with hypertension (BP > 170/110);
• Patients currently on bosentan therapy.
• Use with Alpha-blockers

PDE5 inhibitors, including sildenafil, and alpha-adrenergic blocking agents are both vasodilators with blood-pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes can lower blood pressure significantly, leading to asymptomatic hypotension. In the sildenafil/nitroprusside interaction studies, sildenafil, which may potentiate the hypotensive effect of nitroprusside, was shown to potentiate the hypotensive effects of nitroprusside.

Effects on the Eye

A number of visual disturbances, including headache, nasal stuffiness, and pharyngitis, were reported during these interaction studies. The safety of combined use of PDE5 inhibitors, including REVATIO, with alpha-blockers may be affected by other variables, including intravascular volume depletion and concomitant use of antihypertensive drugs.

CONTRAINDICATIONS

with-Ritonavir and Other Potent CYP3A Inhibitors

The safety of REVATIO is unknown in patients with bleeding disorders or active peptic ulceration. Ritonavir or other potent CYP3A4 inhibitors (e.g., clarithromycin, atazanavir, indinavir, nefazodone, ritonavir) have been shown to substantially increase serum levels of sildenafil (9% versus 0% placebo and for all sildenafil doses studied was 1.9% versus 0.6% placebo). The incidence of retinal hemorrhage at the recommended sildenafil 20 mg TID dose was 1.4% versus 0% placebo and for all sildenafil doses studied was 1.9% versus 0% placebo. The incidence of eye symptoms was 14.6% versus 0.6% placebo for all sildenafil doses studied and at all doses studied was 1.4% for sildenafil versus 1.4% for placebo. The patients experiencing these events had risk factors for hemorrhage including concurrent anticoagulant therapy.
In a placebo-controlled fixed dose titration study of REVATIO (starting with recommended dose of 20 mg TID and increased to 40 mg TID and then 80 mg TID) as an adjunct to intravenous epoprostenol in pulmonary arterial hypertension, the adverse events that were reported more frequently than in the placebo arm (<4% differences are shown in Table 2).

Table 2. REVATIO-Epoprostenol Adverse Events More Frequent (% >5%) than Placebo

<table>
<thead>
<tr>
<th>ADVERSE EVENT</th>
<th>Placebo (%)</th>
<th>Epoprostenol (%)</th>
<th>Placebo (%)</th>
<th>Epoprostenol (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>34</td>
<td>57</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>13</td>
<td>25</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>16</td>
<td>14</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>6</td>
<td>17</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18</td>
<td>25</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>2</td>
<td>9</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

*Includes peripheral edema

REVATIO injection was studied in a 66-patient, placebo-controlled study at doses targeting 20 mg TID and increased to 40 mg TID and then 80 mg TID (up to 3 times the exposure of the recommended dose). Adverse events in PAH patients were similar to those seen with oral tablets.

Postmarketing Experience

The following adverse reactions have been identified during postmarketing use of sildenafil (marketed for both PAH and erectile dysfunction). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular Events

In postmarketing experience, sublingual at doses indicated for erectile dysfunction, serious cardiovascular, cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, pulmonary hypertension, and subarachnoid and intracerebral hemorrhages have been reported in temporal association with the use of the drug. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of sildenafil without sexual activity. Others were reported to have occurred hours to days after use with concurrent sexual activity. It is not possible to determine whether these events are related directly to sildenafil, to sexual activity, to the patient’s underlying cardiovascular disease, or to a combination of these or other factors.

In drug-drug interaction studies, sildenafil (25 mg, 50 mg, and 100 mg) and the alpha-blocker doxazosin caused a reduction of supine blood pressure that was greater than that seen with placebo. In many cases, medical follow-up of these patients was limited. It is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Nervous system: Seizure, seizure recurrence

DRUG INTERACTIONS

Alcohol

Concomitant use of REVATIO with nitrates in any form is contraindicated [see Contraindications].

Nitrate and other PDE5 Inhibitors

Concomitant use of REVATIO with tadalafil and other PDE5 inhibitors is not recommended [see Warnings and Precautions].

Alpha-blockers

Use caution when co-administering alpha-blockers with REVATIO because of additive blood pressure-lowering effects [see Warnings and Precautions].

Registration Opens for EHR Incentive Programs

BY MARY ELLEN SCHNEIDER

Eliorve Global Medical News

News

Officials in the Office of the National Coordinator for Health Information Technology recently released two surveys showing that more than 40% of office-based physicians and 80% of hospitals plan to seek federal incentives for the adoption and use of EHRs under Medicare and Medicaid.

The incentive programs, which launched at the start of the year, offer payments to physicians for using health information technology (HIT) to improve patient care. The federal government recently issued regulations detailing how physicians and hospitals can meet standards for so-called ‘meaningful use’ of the technology. Physicians who meet the criteria are eligible to receive up to $44,000 over 5 years under the Medicare program or $63,750 in 6 years under the Medicaid program. Eligible hospitals could receive millions of dollars, according to the Centers for Medicare and Medicaid Services (CMS).

The survey of office-based physicians, conducted by the Centers for Disease Control and Prevention, found that 41% plan to achieve meaningful use and seek federal incentive payments. Of those, about 80% said that they plan to enroll during first stage of the program, this year or next year.
Mineral Poses Lung Risk

Eriophytes from page 1

Health became aware of the health problem in 2006, and the following year changed the state’s health regulations to include erionite-containing gravel. The recommendations slowed the use of erionite-containing gravel in North Dakota, but it continued to be shipped out of the state, said Dr. Carbone, director of the Cancer Research Center of Hawaii and professor and chair of pathology at the University of Hawaii, both in Honolulu. After a baseball field with erionite-containing gravel was closed in 2008 in the tiny town of Killdeer, N.D., the Associated Press quoted a state legislator as telling state and federal officials they were making a “mountain out of a molehill with what little data you have” and that taxpayers were having a “tough time trying to swallow this.” One resident said she used the bright white gravel on her flower beds, while an area rancher said concerns over erionite were “one of those sky-is-falling kinds of deals.”

Part of the battle over public opinion may be dust mining. No increase in mesotheliomas has been observed in Dunn County, but we are just now approaching the latency period when cancers would begin to develop, Dr. Carbone said. “We are in the same situation as we were in the United States in the ‘20s and ‘30s with asbestos, and we should not wait for danger to occur to start taking actions to protect public health. There is no excuse based on our current knowledge to play a wait-and-see game.”

Lung screening was offered to Dunn County residents exposed to erionite, but only 34 residents, including gravel pit and road maintenance workers, enrolled in the study. A significant increase in interstitial changes above background prevalence was observed on high-resolution computed tomography in 17.6% of residents, compared with 1.5% for male urban transportation workers with low cumulative asbestos fiber exposure, Dr. Carbone said.

Transmission electron microscopy revealed higher total concentrations of erionite fibers in air samples taken on street-side in Dunn County (mean 0.108 structures per cubic centimeter [s/cc]) compared with samples taken from the streets of five Turkish villages including Boyali (mean 0.00 s/cc), he said. Total TEM erionite concentrations were also higher indoors in Dunn County than in Boyali (mean 0.175 s/cc versus 0.043 s/cc).

Research in Turkey has shown that increased industrialization significantly increases airborne particulates, an observation that is particularly worrisome since oil production activity has increased road traffic in Dunn County. Industrial development has grown in states such as Nevada, where erionite deposits are far more common than in North Dakota.

Equally worrisome is that, unlike asbestos, erionite has no current health benchmarks nor is it regulated by the U.S. Environmental Protection Agency or other agencies, Dr. Miller said. “The horse is out of the barn for some, but I think we can do a lot more to protect others,” he said. “You can’t ban a natural substance, but I’d certainly like to see contaminated materials and disturbance of problem areas managed more effectively.”

Dr. Carbone stressed the need to reduce erionite exposure, but is also working to isolate mesothelioma-susceptibility genes that might help to explain the pathogenesis of the disease and to identify high-risk patients for early treatment. The U.S. Early Detection Research Network, a branch of the National Cancer Institute, has funded a clinical trial that is prospectively evaluating osteopontin and mesothelin as early markers for the detection of mesothelioma. The 800-patient trial is expected to begin in 2011 and to be completed sometime in 2013, said Dr. Carbone, its coprincipal investigator who is working together with thoracic surgeon Dr. Harvey I. Pass, professor and chief of the thoracic surgery division at New York University’s Langone Medical Center in New York City.

Dr. Carbone and his team are also looking to identify some point in the evolution of mesothelioma process that is vulnerable to intervention. Dr. Haining Yang, now also at the University of Hawaii Cancer Center, was the first author of a previous report that tumor necrosis factor-alpha inhibits asbestos-induced cytotoxicity via a nuclear factor-kappa B-dependent mechanism that increases the percentage of human mesothelial cells that survive asbestos exposure, thus increasing the pool of asbestos-damaged cells susceptible to malignant transformation (Proc. Natl. Acad. Sci. USA 2006; 103:1097-402).

When the investigators looked at tissue culture, North Dakota, Oregon, and Turkish erionite were found to induce high-mobility group protein Bi (HMGB1) and TNP-alpha release from human mesothelial cells and macrophages, Dr. Yang and colleagues also reported. When coupled with chronic inflammation of the peritoneum and pleura, HMGB1 and TNP-alpha release have been linked to malignant mesothelioma in mice and in humans (Proc. Natl. Acad. Sci. USA 2010;107:12611-6).

Dr. Carbone called for a larger, more detailed epidemiologic survey of the health implications of erionite in North Dakota, as was performed for Libby, Mont., and said that it should include mine and road workers with direct exposure as well as adults and children with environmental exposure. This survey also should include correlative studies that exploit recent findings regarding biomarkers involved in fiber carcinogenesis, as is being done in Libby, he said.

The study was partially funded by a National Cancer Institute investigator grant.

Dr. Carbone and Dr. Miller noted no conflicts of interest. Coauthors reported funding from Rosetta Genomics, Celera, Soma Logic, and SourceMDX, and one reported having a leadership role in the American College of Radiology Imaging Network.

Allegro Now Available OTC

Beginning on March 4, Allegro (fexofenadine hydrochloride) allergy relief products will be available without a prescription.

Sanofi-Aventis announced that the U.S. Food and Drug Administration has approved over-the-counter status for Allegro 12- and 24-hour tablets for patients aged 12 years and older, Children’s Allegro 12-hour tablets and oral, dissolving tablets for children aged 6 years and older, and Allegro liquid for children aged 2 years and older.

According to the company, the FDA also approved behind-the-counter sale of Allegro-D 24-hour and 12-hour extended-release tablets, which include the decongestant pseudophedrine, for patients older than 12 years.

The approval for OTC Allegro is for the same rhinitis indication as the prescription version.

According to its Web site, Allegro will be the “only over-the-counter allergy brand without a drowsiness warning.”

“The Pink Sheet” is published by Elsevier.
More Dangerous Form of Plaque Linked to OSA

It is a disease of obesity, and 30% of Americans are obese, Dr. Schoepf said. Diminishing the oxygen supply exposes the cardiovascular system to oxidative stress, and may render vessel linings more vulnerable to the formation of atherosclerosis. OSA has been linked to coronary artery disease, he noted.

Computed tomography is the only noninvasive test that can directly evaluate cardiac valve patency and analyze the composition of atherosclerotic lesions on vessel walls, Dr. Schoepf said. Therefore, it was used to study the association between OSA and coronary artery disease.

Investigators performed a retrospective search for patients who had undergone CT of the heart and polysomnogram assessment for suspected OSA. One observer measured coronary artery calcium, known informally as hard plaque. Two observers in consensus analyzed heart CT data for the presence and degree of coronary artery narrowing or blockages. The presence and extent of noncalcified or “soft” plaque, also known as vulnerable plaque, were also evaluated. Noncalcified plaque frequently causes acute cardiac events such as heart attack and unstable angina.

The retrospective search revealed 97 patients who had undergone both heart CT and polysomnography. The two observers excluded because their polysomnogram was performed more than 36 months before or after the date of their cardiac CT. The mean apnea-hypopnea index score in this patient cohort was 27.3 (moderate).

Of the 95 remaining patients, 49 (23 women, mean age 61 years, average body mass index 33 kg/m²) had documented obstructive sleep apnea by polysomnogram. The other 46 patients (24 women, mean age 60 years, average body mass index 30 kg/m²) were found not to have obstructive sleep apnea by polysomnogram.

The investigators found no significant difference in age, gender, body mass index, or cardiovascular risk factors between the two groups.

Agatston calcium scores (which are a measure of hard plaque) were not significantly different between the two groups (mean score 272 for the group with OSA versus 241 for those without OSA, P = .5).

The presence of any type of narrowing in the heart vessels was found to correlate with the presence of obstructive sleep apnea (P < .0001).

The total number of heart vessels with any narrowing was also found to correlate with the presence of obstructive sleep apnea (P = .0008).

In addition, the degree of narrowing in the highest grade of lesion correlated with obstructive sleep apnea (P = 0.013).

The presence of noncalcified plaque (soft or vulnerable plaque) had a significant correlation with the presence of obstructive sleep apnea in this study, Dr. Schoepf said.

If the study’s findings are sustained by larger prospective trials in the future, cardiac CT could emerge as a useful noninvasive tool for investigating the relationship between obstructive sleep apnea and coronary artery disease, he concluded.

### Coronary CT angiography revealed the presence of soft plaque and narrowing in the heart vessels of patients with obstructive sleep apnea.

### CT angiograms of heart vessels show calcified plaque (arrows, both images) and soft plaque (arrowheads, left image) in a patient with OSA.

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Phrenic Nerve Stimulation Shows Early Promise in CSA

Phrenic nerve stimulation (PNS) has the potential to treat chronic obstructive sleep apnea (CSA), and is currently approved for use in treating patients with central sleep apnea (CSA). It was developed by Cheyne-Stokes breathing with oxygen desaturation, central apneic episodes, and disrupted sleep architecture. PNS was found to improve overnight sleep studies. On one night, patients received no treatment. On the other night, they received phrenic nerve stimulation with the generator remaining outside the body.

Three patients then underwent implantation of the full RespCardia system. After a month-long healing period during which the system remained off, they returned for two overnight sleep studies: the first with the system off, the second with it switched on for the first time. A month later they were back in the sleep lab for another overnight study—this time to assess the effects of 1 month of treatment, explained Dr. Abrahm, professor of internal medicine, physiology, and cell biology. The device was placed in the azygos vein. The pulse generator can be placed in the azygos vein to monitor respiration.

Dr. Abraham reported at the annual scientific session of the American Heart Association.

In the study’s acute phase, 13 heart failure patients with central sleep apnea (CSA) marked by Cheyne-Stokes breathing with oxygen desaturation, central apneic episodes, and disrupted sleep architecture underwent two overnight sleep studies. On one night, patients received no treatment. The other night, they received phrenic nerve stimulation with the generator remaining outside the body.

Three patients then underwent implantation of the fully implantable phrenic nerve stimulator and transvenous stimulation lead, Dr. William T. Abraham reported at the annual scientific session of the American Heart Association.

The pulse generator can be implanted in the azygos vein to monitor respiration. Dr. Abraham said the next step in the development of the RespCardia system is to determine whether the improvements in oxygenation, sleep architecture, and central apneic episodes seen in this preliminary study are maintained over longer periods, and more importantly whether these sleep benefits translate into improved heart failure status and quality of life.

He said that he serves as a modestly compensated consultant to Cardiac Concepts, which sponsored these studies and is developing the RespiCardia system.
Microscopic Invasion May Predict Lung Ca Survival

**By Patrice Wendling**

_Elsevier Global Medical News_

CHICAGO – New data suggest that microscopic vascular invasion may be a more powerful prognosticator in early lung cancer than are the tumor size-based categories suggested in the new TNM staging system.

Researchers used histologic and immunohistochemical techniques to identify microscopic vascular invasion (MVI), or the presence of neoplastic structures inside the lumen of a vessel, in one-third (154 of 512) patients with resected, pathologically staged T1a to T3 node-negative non-small cell lung cancer (NSCLC). The 2009 edition of the tumor, node, metastasis (TNM) staging system for lung tumors was used.

MVI was significantly correlated with the presence of tumor-infiltrating lymphocytes (odds ratio 1.65, P = .03), adenocarcinoma histology (OR 1.32, P = .005), and increased tumor size (OR 1.13, P = .009).

Five-year overall survival was significantly lower for patients with MVI at 50% vs. those without MVI at 66% (P = .001), Dr. Enrico Ruffini said at the Chicago Multidisciplinary Symposium in Thoracic Oncology.

The difference in survival remained significant even in those with squamous cell carcinoma (49% vs. 61%, P = .05), although it was more pronounced in those with adenocarcinoma (56% vs. 70%, P = .03). “Microscopic vascular invasion is a significant independent negative prognostic factor,” he said.

When patients with pT1a-T2b tumors were stratified by T-size category, the presence of MVI resulted in a one-category upstaging for each T category, said Dr. Ruffini of the division of thoracic surgery at the University of Torino (Italy). For example, T1a patients with MVI had a prognosis similar to that of patients with T1b tumors without MVI. The number of T3 cases was too small to stratify by T size.

Five-year overall survival was 50% vs. 75% vs. 95% with no MVI, one MVI, and two or more MVI, respectively (P = .003), he said.

Moderate or severe invasion of the vascular wall was seen in 40% of MVI-negative cases vs. 64% in MVI-positive cases (P = .001). “The invasion lies in a distinct subpopulation of the cell and is selected out under pressure,” he said.

The 2009 TNM stresses the importance of tumor size as a major prognostic factor, but no TNM edition has so far included MVI as a major determinant in the staging of NSCLC.

In a multivariate survival analysis that included age, sex, histology, grading, T-size determinant, MVI, perineural invasion, and tumor-infiltrating lymphocytes, MVI was a stronger prognostic indicator (hazard ratio 1.43, P = .02) than was T-size determinant (HR 1.06, P = .06), Dr. Ruffini said.

Invited discussant Dr. Mark Socinski pointed out that 88% of patients in the analysis had 5 cm or smaller tumors, a category of patients in whom adjuvant therapy has been discouraged. He highlighted a recent meta-analysis of 4,584 NSCLC patients in five cisplatin-based adjuvant chemotherapy trials that showed an overall significant survival benefit of 4% at 5 years, but also a potentially negative effect in resected stage IA disease (Ann. Oncol. 2010;Suppl. 7:vii196-8).

“We need to make sure [MVI] is easily reproducible amongst pathologists, and we also clearly need to demonstrate that adjuvant therapy can overcome the biological impact of this histopathologic finding,” said Dr. Socinski of the Lineberger Comprehensive Cancer Center at the University of North Carolina, Chapel Hill.

Although rebiopsy is not common practice, invited discussant Dr. Mark Socinski said it should be on the clinicians’ radar because it can alter the therapeutic course of refractory disease and arguable the clinical benefit.

“I think the message here is to consider rebiopsy more often in selected patients until we have a better understanding of this one disease we call non–small lung cancer, since we realize it is an incredibly heterogeneous disease,” said Dr. Socinski, director of the multidisciplinary thoracic oncology program at the Lineberger Comprehensive Cancer Center at the University of North Carolina–Chapel Hill.

Among the five patients whose cancer transformed, two maintained a slow, indolent course after SCLC transformation, while three had a change around the time of their biopsy to an explosive growth pattern more clinically reminiscent of SCLC, Dr. Sequist said. Four patients were treated with SCLC-like chemotherapy regimens, and three responded with marked partial responses.

“Longitudinal data from fluorescent in situ hybridization analysis for MET and EGFR gene copy number suggest that the resistant tumor is distinct from the original tumor and that MET amplification lies in a distinct subpopulation of the cell and is selected out under pressure from TKI therapy, she said.

Multiple biopsies over time also identified a waning and waning of genotypic and phenotypic findings in response to selective pressure of TKI therapy. This pattern was most pronounced in a case that transformed from EGFR TKI-sensible adenocarcinoma to resistant SCLC while on erlotinib (Tarceva) for more than 1 year, switched back to TKI-sensitive adenocarcinoma following concurrent chemotherapy and radiation and a 9- to 10-month break from erlotinib, and then after a very successful but short-lived response to erlotinib, shifted back to SCLC a second time under erlotinib.

“It’s showing us that if you do repeat biopsies, it can direct patients toward clinical trials that they have a higher likelihood of benefiting from,” said Dr. Sequist. “It’s a really a nice thing to be able to offer patients.”

The population comprised 15 men and 22 women. All patients, median age 60 years, had clinically responded to either gefitinib (Iressa) or erlotinib, with a median of 18.4 months of initial EGFR TKI therapy (range 4-69 months). The majority, or 81%, remained on TKI at the time of repeat biopsy. Repeat biopsy showed T790M mutations in 49%, PIK3CA in 5%, MET amplification in 5%, and an unknown mechanism in 30%, reported Dr. Sequist at the symposium, cosponsored by the American Society of Clinical Oncology, American Society for Radiation Oncology, International Association for the Study of Lung Cancer, and University of Chicago.

Dr. Sequist and Dr. Socinski disclosed no relevant conflicts. Two coauthors have submitted a patent for genotyping methods.
Anti-TNF-Alpha Timing, Type Linked to *L. pneumophila*

**BY DIANA MAHONEY**

Elsivier Global Medical News

BOSTON – The risk of Legionnaires’ disease associated with tumor necrosis factor–alpha antagonist therapy is greatest during the first year of treatment and is significantly higher for patients receiving adalimumab or infliximab compared with etanercept, according to a study reported at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy.

Using data from the RATIO registry, Dr.anny Lanternier of the Nécker Hospital for Sick Children in Paris and colleagues conducted an incidence and risk factor study to investigate the relationship between the three drugs included in the registry – adalimumab, infliximab, and etanercept – and *Legionella pneumophila* infection, which they previously reported in patients receiving anti-tumor necrosis factor-alpha (anti-TNF-alpha) treatment. The prospective French RATIO (Research Axed on Tolerance of Biotherapies) registry was designed to collect information on opportunistic and severe bacterial infections and lymphoma in patients treated with anti-TNF-alpha agents. The researchers used the French population as the reference population, as the French RA treatment registry was designed to include cases of *L. pneumophila* infection, which they previously reported in patients receiving anti-TNF-alpha drugs, according to Dr. Lanternier.

From January 1, 2004, to January 1, 2007, the RATIO registry received reports of 27 cases of laboratory-confirmed *L. pneumophila* infection. “The overall annual incidence rate of infection for patients on anti-TNF-alpha therapy, adjusted for age and sex, was 47.1/100,000 patients per year, which represents a 13-fold increased risk, compared with the reference population,” Dr. Lanternier reported. When evaluated by agent, the standardized incidence risk was significantly higher, at 22.3, for patients taking infliximab or adalimumab – both anti-TNF-alpha monoclonal antibody agents – compared with 3.0 for patients taking etanercept, which is a soluble TNF-alpha receptor therapy, she said at the meeting, which was sponsored by the American Society for Microbiology.

**Risk of *L. pneumophila* infection is greatest during first year of treatment with adalimumab or infliximab.**

Similarly, in the case-control analysis, exposure to adalimumab or infliximab was an independent risk factor for *L. pneumophila* infection, as was the first year of anti-TNF-alpha treatment, Dr. Lanternier said. Compared with patients with *L. pneumophila* infection in the French population, anti-TNF-alpha–treated patients with the infection were younger and had a markedly lower infection-related mortality rate at 3.7% vs. the 10%-20% observed in the population not treated with anti-TNF-alpha drugs, said Dr. Lanternier, attributing the difference to the probability that the immunosuppressed patients are more closely monitored.

In a separate study, Dr. Alfred F. Sobotto, medical officer for the U.S. Food and Drug Administration, reported an association between *L. pneumophila* infection-mortality and onset of the infection within 90 days of initiating anti-TNF-alpha therapy in patients of younger mean age receiving concomitant therapies.

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Evidence for Smoking–Severe RA Link Strengthened

BY JENNIE SMITH
Elsevier Global Medical News

Smoking is implicated in more than a third of cases of the most severe and common form of rheumatoid arthritis, researchers in Sweden have found, and in one in five cases of RA overall.

Results from a population-based study strengthened the growing body of evidence that links smoking with development of anti-citrullinated protein/peptide antibody (ACPAs)-positive rheumatoid arthritis. In a dose-response manner, the link became stronger with heavier smoking, regardless of age status.

The investigators, led by Henrik Källberg, Ph.D., of the Karolinska Institute in Stockholm, determined the excess fraction of RA cases attributable to smoking to be 20%, regardless of the presence of known genetic risk factors, which comprise single or dual copies of the HLA-DRB1 shared epitope.

Smoking was estimated to be responsible for 35% of ACPA-positive cases (31% for women and 42% for men), and for each copy of the HLA-DRB1 shared epitope (SE) that was found, smoking was dose-dependently associated with an increased risk of ACPA-positive RA. In people with two copies of the HLA-DRB1 SE, 55% of ACPA-positive RA was attributable to smoking, Dr. Källberg and colleagues found (Ann. Rheum. Dis. 2010 [doi:10.1136/ard.2009.120899]).

Dr. Källberg and colleagues also found an increased risk of developing RA (OR, 1.9; 95% confidence interval, 1.1-3.5) among heavy smokers without any genetic risk factors. “That was one really interesting finding,” Dr. Källberg said in an interview. “As a heavy smoker, you are almost two times more likely to develop RA even without the HLA-DRB1 SE alleles, he said.

For their research, Dr. Källberg and colleagues collected blood samples and questionnaire information from 1,205 people who were diagnosed with RA according to the American College of Rheumatology’s 1987 criteria, as well as 872 healthy controls matched for age, sex, and geographic location. The cases were part of the Swedish EIRA (Epidemiological Investigation of Rheumatoid Arthritis) cohort study.

The questionnaires solicited information on past and current smoking, thereby allowing investigators to classify each subject by smoking history (current and former smokers of 0-9, 10-19, and 20 pack-years, with 1 pack-year defined as equaling 20 cigarettes per day for 1 year).

The investigators tested blood samples for ACPA status and the presence of genotyped SE alleles.

The investigators calculated the odds ratios of developing RA associated with different smoking levels and SE alleles, together with 95% confidence intervals, by using logistic regression models.

The interaction between smoking and the presence of SE alleles was evaluated as a departure from additive effects, and was estimated by calculating the attributable proportion due to interaction.

For former light and moderate smokers, the risk of developing RA declined and approached never-smoker levels the longer the person had not smoked since quitting. Former heavy smokers, however, continued to see elevated risk, even decades after quitting.

The dose-dependent association with smoking was “not a total surprise. We knew from earlier studies that there was some sort of relationship with the amount,” Dr. Källberg said. “We just didn’t expect it to be so clear cut.”

The fact that ex-heavy smokers continued to see elevated risk does not mean that smokers shouldn’t quit, Dr. Källberg said. “The time frame, the damage may be done, but we actually find that you gain something by quitting smoking. Quitting smoking can affect how well you respond to treatment.”

Although smoking’s presence in RA is smaller than in lung cancer, it is “similar to that seen for ischemic heart disease,” the investigators wrote in their analysis. Furthermore, cardiovascular disease is associated with RA and is the major cause of premature death in people with RA, according to the investigators.

Dr. Källberg and colleagues noted that some other factors, such as air pollution, alcohol consumption, and hormonal differences could affect the smoking-RA interaction among populations. However, they wrote, they were confident—based on the age, sex, and residential matching of controls and cases within the same population—that their methodology was strong.

Dr. Källberg and colleagues’ study was funded by grants from the Swedish government, the insurance company APA, the European Union; the Flight Attendant Medical Research Institute; National Institutes of Health; and the COMBINE (Controlling Chronic Inflammatory Diseases With Combined Efforts) project. Neither Dr. Källberg nor any of his colleagues declared any conflicts of interest.

Hypothyroidism Risk Rises With Recent Smoking Cessation

BY MICHELE G. SULLIVAN
Elsevier Global Medical News

PARIS – Smokers who have recently kicked the habit could face a significant increase in the risk of developing new-onset hypothyroidism.

The risk is greatest within the first 2 years of quitting, when it can run as high as five times the risk of someone who has never smoked, or who has been tobacco-free for more than 2 years.

There’s no obvious explanation for the phenomenon, Dr. Allan Carle said at the International Thyroid Meeting. However, he said, a 2007 study suggests that current smokers actually have a significantly lower risk of developing hypothyroidism but an increased risk of hyperthyroidism (Arch. Intern. Med. 2007;167:1428-32).

“Perhaps quitting causes some kind of rebound effect, with changes in antithyroid antibodies,” said Dr. Carle of the Aalborg Hospital, Denmark. But his case-control study could only observe the phenomenon—not uncover its possible cause.

He and his associates compared 140 patients with incident autoimmune thyroid hypothyroidism, extracted from a population-based study, to 560 age- and sex-matched controls from the same population.

All the subjects provided information on their smoking status, including daily and overall tobacco intake, years of smoking, pack-years of smoking, and—if they were past smokers—the time since quitting. Clinical measurements included autoantibodies to thyroid peroxidase (TPOAb) and thyroglobulin (TgAb); thyroid function; and a thyroid ultrasound exam. Possible relationships were examined in both univariate and multivariate models that controlled for confounding.

The investigators used the group of never-smokers as the reference group. The risk of hypothyroidism among current smokers and those who had quit more than 2 years before the study was not significantly different from the risk among never-smokers. There were also no significant relationships between new hypothyroidism and the duration or magnitude of smoking.

However, among subjects who had quit within the past 2 years, the risk of new hypothyroidism was significantly increased. Those who had quit within the past 1 year were 3.6 times as likely as never-smokers to develop the disorder; those who had quit 1-2 years before were 5 times as likely to develop it.

The risk of new-onset hypothyroidism dropped back to the reference range for those who had quit smoking 3-10 years before the study (odds ratio 0.85).

“Recent quitters were also more hypothyroid than other study subjects who had hypothyroidism,” Dr. Carle said. Those who had quit within the past 2 years had a median total T4 level of 20 nmol/L, compared with 40 nmol/L in never-smokers with the disorder, and a median T3 level of 82 mU/L vs. 49 mU/L.

“Looking at these data, we can say that in this series, 13% of new-onset hypothyroidism was associated with smoking withdrawal,” Dr. Carle said. Because of this association, he recommended thyroid testing for all patients who report recent smoking cessation, “especially in those who have any complaints of symptoms.”
Designed to deliver improved fat absorption... 
- Mean coefficient of fat absorption (CFA) was 88.3% for patients treated with ZENPEP vs 62.8% for patients treated with placebo (primary endpoint) in the pivotal trial of patients aged ≥7 years.
- 91% (n=29 of 32) of patients achieved a CFA >80%.
- Results were achieved without the use of concomitant agents such as PPIs, H₂-antagonists, and motility agents.

...with improved symptom control, even when switched from a previous enzyme.
- 100% (N=19) of children with PI due to CF switched to ZENPEP from a previous unapproved pancreatic enzyme had improved or maintained their level of symptom control (secondary endpoint).
  - In this open-label, uncontrolled trial of patients aged 1 to 6 years, parents/guardians reported that 47% of patients switched to ZENPEP had improved symptom control (n=9) and 53% maintained symptom control (n=10).
  - ZENPEP is not interchangeable with any other pancrelipase product, and requires a new prescription.

Important Safety Information
- Exercise caution when prescribing ZENPEP to patients with gout, renal impairment, or hyperuricemia and when administering pancrelipase to a patient with a known allergy to proteins of porcine origin.
- Fibrosing colonopathy is a rare serious adverse reaction associated with high-dose use of pancreatic enzyme replacement products and most commonly reported in pediatric patients with CF. Exercise caution when doses of ZENPEP exceed 2500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of body weight per day).
- To avoid irritation of oral mucosa or inactivation of enzymes, do not chew ZENPEP capsules or beads or retain in the mouth.
- There is theoretical risk of viral transmission with all pancreatic enzyme products, including ZENPEP.

References:

*Reports were subjective and recorded in a daily diary form.
PULMONARY MEDICINE

BY SUSAN LONDON
Elsevier Global Medical News

VANCOUVER, B.C.—Chest physicians must take a slew of diagnostic possibilities when evaluating patients with rheumatoid arthritis who have developed pulmonary abnormalities, according to Dr. Kevin R. Flaherty, FCCP. “We have to keep in mind all the different things that can go wrong in these patients when we are trying to treat them: Is this progression of the underlying disease? Is this a complication of the therapy? Or is this the development of something new, like a cancer, that’s now causing the patient’s symptoms?” he said to attendees of CHEST 2010, the annual meeting of the American College of Chest Physicians.

Pulmonary Manifestations of RA

“The lung is a common site for extra-articular rheumatoid arthritis,” noted Dr. Flaherty, who is a pulmonologist and associate professor at the University of Michigan Health System in Ann Arbor. Of the many pulmonary manifestations of RA, interstitial lung disease causes the greatest morbidity and mortality. The lifetime risk of interstitial lung disease is nearly 8% in patients with RA, compared with 1% in the general population (Arthritis Rheum. 2010;62:1583-91). And this disease confers a poor prognosis, with a near tripling of the risk of death and with a median survival after diagnosis of only about 2.5 years.

High-resolution CT (HRCT) and pulmonary function testing appear to be useful for identifying interstitial lung disease early in its course, Dr. Flaherty said. For example, among patients within 2 years of an RA diagnosis, 44% have been found to have HRCT, pulmonary function test, and other abnormalities consistent with interstitial lung disease in the absence of symptoms (Am. J. Respir. Crit. Care Med. 1997;156:528-35).

“The [HRCT] features were mild—reticular thickening, ground glass, and not much honeycombing—suggesting maybe that we might be able to impact the disease, because I think once you get to honeycomb lung and end-stage fibrosis, our ability to impact this disease is likely to be lower,” he said.

Another study among patients with recent-onset RA found abnormalities on HRCT but normal results on pulmonary function tests (Scand. J. Rheumatol. 2007;36:338-44), “suggesting that symptoms and pulmonary screening are not going to be as sensitive as HRCT screening.”

As for which patients to screen for interstitial lung disease, the predictors of abnormal pulmonary function testing in the RA population are respiratory symptoms, smoking, anti-cyclic citrullinated peptide positivity, and use of prednisone (Arthritis Res. Ther. 2010;12:R104).


“We are starting … to see data emerging that really mirrors what we see in idiopathic lung disease, that the histopathology and the CT appearance can help us in terms of stratifying patients for risk of subsequent mortality,” Dr. Flaherty said.

For example, a study of patients with RA-associated interstitial lung disease found 50% mortality in those with a usual interstitial pneumonia (UIP) histology, compared with none in those with a nonspecific interstitial pneumonia (NSIP) histology after a similar median follow-up of about 4 years (Chest 2005;127:2019-27).

A honeycomb pattern on HRCT was found only in the UIP group, suggesting that this radiographic pattern is a good surrogate for this histology, Dr. Flaherty noted. And indeed, patients having a definite UIP radiographic appearance have poorer survival (Eur. Respir. J. 2010;35:1322-8).

Continued on following page
Rigorous studies are lacking when it comes to treating sarcoidosis or modest – and this requires a discussion with the patient – then I think the observation is completely reasonable," Dr. Culver said.

In more severe cases, the algorithm proposes short-course, moderate-dose therapy with prednisone 20-30 mg daily for 3-4 weeks, as supported by several studies, including a recent one among patients with acute exacerbations (Ann. J. Med. Sci. 2010;339:1-4). "Be less aggressive with your steroid dosing," he recommended. "You can really get away with shorter courses, with lower doses than we have been using in the past."

For patients who have a good response, the goal is to taper to 10 mg daily or less, a practice endorsed by a Delphi consensus study of sarcoidosis management (Respir. Med. 2010;104:717-23). When patients have an inadequate response to prednisone or are unable to reduce the dosage to 10 mg daily, the algorithm suggests adding an immune modulator (methotrexate, azathioprine, leflunomide, or mycophenolate).

If you can hold off on treating, you may be able to prevent side effects from medicines ... and still have a patient who has corticosteroids, the best therapy is no therapy coupled with close observation.

If the symptoms are relatively mild or modest ... observation is completely reasonable.**

If the symptoms are relatively mild or modest ... observation is completely reasonable.**

In one study, 39% of patients with stage 2 or 3 disease on chest x-ray had neither progression nor improvement during a 6-month period. When these stable patients were assigned either to immediate treatment with a fairly aggressive regimen of prednisolone or to as-needed treatment only if spirometry showed deterioration, just 19% of the latter group required treatment during the next 5 years (Thorax 1996;51:238-47).

"If you hold off on treating, you may be able to prevent side effects from medicines ... and still have a patient who has corticosteroids, the best therapy is no therapy coupled with close observation."

Continued from previous page

Rigorous studies are lacking when it comes to treating interstitial lung disease in the RA population, he said. Case reports, case series, and retrospective analyses have assessed many immunomodulating and immunosuppressive agents, but "what we are really begging for are some prospective, well-done clinical trials to help us sort all of these potential treatments out."

Pulmonary Side Effects of RA Therapy

Anti-tumor necrosis factor (TNF) agents such as infliximab have been associated with pulmonary adverse effects and complications, including infection, pulmonary hypertension, and lupus pneumonitis.

Some reports have also raised concern that anti-TNF agents may hasten progression of interstitial lung disease in patients with RA and thus increase mortality. "The data on that are still out," Dr. Flaherty said. Evidence thus far suggests that mortality in patients treated with these agents is similar to that in their counterparts treated with traditional disease-modifying antirheumatic drugs (Ann. Rheum. Dis. 2010;69:1086-91). Rituximab has been linked to serious infections in RA patients, most of which (40%) were pneumonitis. Only a small number of patients developed methotrexate toxicity, Dr. Flaherty pointed out.

Pulmonary Cancers

Patients with RA have increased risk of lung cancer (standardized incidence ratio, 1.63) as well as for another malignancy that can involve the lung, mesothelioma (Arthritis. Res. Ther. 2008;10:R45), as a result of their underlying disease, long-term immunosuppression, or both.

Treatment with biologic agents has not been associated with a significantly elevated risk of lung cancer among patients with RA, Dr. Flaherty said. But treatment with methotrexate has, with the incidence of lung cancer among mesothelioma cases increasing for users under triple that of the general population (Arthritis Rheum. 2008;59:794-9).

"So as we are seeing [patients] with pulmonary manifestations, we have to keep in mind their risk of cancers as well," he recommended. Dr. Flaherty had no disclosures. **
For patients with suspected non–small cell lung cancer, adding endosonography before surgical staging improves detection of mediastinal nodal metastases, thus reducing unnecessary thoracotomies by more than half, a study has shown.

In addition, because endosonography is minimally invasive, adding this step doesn’t raise the rate of complications for staging procedures, said Dr. Jouke T. Annema of Leiden (the Netherlands) University Medical Center and associates.

The researchers compared surgical staging alone to endosonography followed by surgical staging because “at present it is not known whether initial mediastinal tissue staging of lung cancer by endosonography improves the detection of nodal metastases.” Failure to detect such metastases during staging results in patients undergoing thoracotomy for tumor resection, only to have the thoracotomy aborted when unresectable or metastatic lung disease is discovered (JAMA 2010;304:2245-52).

The investigators randomized 241 patients suspected of having resectable lung cancer treated between 2007 and 2009. They were assigned to surgical staging alone, sparing them from further unnecessary thoracotomy.


Disclosures: This study was supported in part by Hitachi Medical Systems, COOK, Olympus, the Zorgprogramma Oncologie Gent, the U.K. National Health Service R & D Health Technology Assessment Program, and the National Institute for Health Research Cambridge Biomedical Research Centre.

Major Finding: Performing endosonography to detect mediastinal node metastases before conducting surgical staging identifies more patients with metastases than does surgical staging alone, sparing them from further unnecessary thoracotomy.

Discussions: This study was supported in part by Hitachi Medical Systems, COOK, Olympus, the Zorgprogramma Oncologie Gent, the U.K. National Health Service R & D Health Technology Assessment Program, and the National Institute for Health Research Cambridge Biomedical Research Centre.

This study was supported in part by Hitachi Medical Systems, COOK, Olympus, the Zorgprogramma Oncologie Gent, the U.K. National Health Service R & D Health Technology Assessment Program, and the National Institute for Health Research Cambridge Biomedical Research Centre.

Dr. Richard Fischel, FCCP, comments: The authors address a very important aspect regarding staging of lung cancer using endosonography; also known as EBUS or endobronchial ultrasound. They describe prethoracotomy staging to help avoid unnecessary thoracotomies, which is an important concept in the treatment of lung cancer. The data do indicate that adding EBUS to the preoperative staging protocol is beneficial, resulting in improved sensitivity for the detection of metastatic disease. It is very likely that preop EBUS may become the standard of care in lung cancer surgery, however, at this time mediastinoscopy remains the gold standard.
Blast Lung, Home Care Equipment, Fibrosis

Disaster Response
Blast Lung Injury

Many of the terrorist acts across the world have increased the awareness of injuries from explosive detonations that release energy at supersonic speeds from the epicenter of the blast. This blast event contributes to primary blast injuries that often affect the head, ear, abdomen, and lung. Secondary injuries may also occur as a result of bomb fragments and other debris that are thrown out. It can also result in tertiary injuries to the individual if he or she gets thrown out from the blast, resulting in head injuries and bone fractures. Other blast-related injuries that are not due to the above mechanisms are referred to as quaternary injuries, and they include burns and exacerbation of previous medical conditions.

Blast lung injury is one of the major causes of morbidity and mortality among the victims of explosion. The incidence of pulmonary blast injury varies from 17% to 63%. There is tissue damage from the pressure changes, and the severity depends on factors such as the explosive used, intensity of the blast wave, its duration, and the proximity of the victim to the epicenter of blast. Pulmonary contusion, hemorrhage, and edema are seen from parenchymal and vascular damage. Blast lung can be associated also with pneumothoraces, hemothoraces, bronchopleural fistula, air/parietal embolization, and other pleural and parenchymal injuries. Body armor may not protect against blast lung injury. Pulmonary symptoms may include cough, dyspnea, chest pain, and hemoptysis. On physical examination, aphonia, tachypnea, cyanosis, cough, wheezing, and/or decreased breath sounds may be present. Blast lung is suspected when patients present with respiratory difficulty and hypoxemia without external chest injury. The key aspects of management are maintaining oxygenation, careful fluid resuscitation, addressing pneumo-/hemorrhages, and initiating mechanical ventilation for respiratory failure.

Dr. Angelina A. Lazarus, FCCP
Vice-Chair

Home Care
CMS Competitive Bidding Program: What the Pulmonologist Should Know

It was hoped that the Medicare Modernization Act would reduce costs and improve access to home care medical equipment through a competitive bidding process. Centers for Medicare & Medicaid Services (CMS) accepted bids covering respiratory home care equipment for nine areas (Cincinnati, Cleveland, Charlotte, Dallas, Kansas City, Miami, Orlando, Pittsburgh, and Riverside, CA) starting January 2011. To obtain a list of vendors, access the medicare.gov site, and the Resource Locator will allow matching of patient zip code and the appropriate approved vendor. Current patients using oxygen/PAP whose suppliers have not been contracted under the competitive bidding program, have the option to continue renting with their current providers as “grandfathered suppliers.” When traveling, patients will need to use contracted suppliers when they are in an area that is covered under the competitive bidding program.

Each contracted supplier is required to list the manufacturers and products they provide. Physicians should be specific when prescribing, including giving reasons that a product should be used. Not all approved providers are able to provide all products; it is possible that a patient could require multiple providers. In home training is not a mandated component of the bidding process. If physicians would like patients to have education in their home, they will need to be very specific when scripting.

This is a dramatic change in how home respiratory care is provided. Physicians should document complications if access to care is limited or if patient care is affected. The program will be expanded to an additional 91 cities starting in January 2013. Now is the time for caregivers, durable medical providers, and Medicare to learn and correct problems, as delivery of home care moves to this new model.

Dr. Lisa Wolfe, FCCP
Vice-Chair

Interstitial and Diffuse Lung Disease
Recent Advances in the Epidemiology of Pulmonary Fibroses

Following is a summary of my presentation given at the Interstitial and Diffuse Lung Disease Network Open Meeting at CHEST 2010. To view the slide presentation, please visit www.chestnet.org/accc/presentations/network-special-presentations-chest-2010. Prior epidemiologic investigations of idiopathic pulmonary fibrosis (IPF) have been limited due to its relative rarity. However, the evaluation of death certificate data provides an opportunity to investigate pulmonary fibrosis (PF) from an epidemiologic perspective in order to identify trends in disease-related mortality and to better understand the burden of disease. Using data from the US Multiple Cause-Of-Death Mortality Database (Centers for Disease Control and Prevention, National Center for Health Statistics, www.cdc.gov/nchs), our group recently reported that mortality rates from PF have significantly increased from 1992 to 2003 in both men (28.4%) and women (41.3%), and are predicted to continue to rise into the future (Olson et al. Am J Respir Crit Care Med. 2007;176[3]:277). Our results parallel the data from other recent epidemiologic investigations that indicate the incidence of disease is also increasing (Coultau et al. Am J Respir Crit Care Med. 1994;150[4]:967; Rha;e et al. Am J Respir Crit Care Med. 2006;174[7]:810; Griffin et al. Thorax. 2006;61[11]:980). At the same time, more patients are dying of the disease itself rather than from comorbid conditions (Olson et al. Am J Resp Cr. Crit Care Med. 2007;176[3]:277; Mannino et al. Am J Resp Crit Care Med. 1996;153[5]:1548; Panos et al. Am J Med. 1990;88[4]:396; Martinez et al. Ann Intern Med. 2005;142:963). Further, mortality rates from PF, like chronic obstructive lung disease, exhibit significant seasonal variation with a significantly higher number of deaths in the winter (17.1%, P less than .0001), followed by spring (12.7%, P less than .0001) when compared with summer months, even in the absence of recognized infection (Olson et al. Chest. 2009;136[1]:16). These results do not appear to be limited to idiopathic disease, as the prevalence of interstitial lung disease in decedents with rheumatoid arthritis has also increased over time despite an overall decline in RA-associated mortality (Olson et al. Am J Resp Crit Care Med. 2010; Sep 17 [Epub ahead of print]). Overall, these trends may represent an increase in the clinical recognition of interstitial lung disease, or perhaps they reflect the lack of effective therapies for lung fibrosis. Regardless of cause, these recent epidemiologic investigations do reveal a rapidly growing problem that deserves further research into the mechanisms of and potential therapies for lung fibrosis.

Dr. Amy Olson
Network Member

CHEST 2011
Opportunities

Call for Abstracts
Submit an abstract of your original investigative work for presentation at the meeting. Submission is free to ACCP members.
• Gain international exposure by presenting to an audience of pulmonary, critical care, and sleep medicine specialists.
• Compete for THE CHEST Foundation investigative awards.
www.acccmeeting.org
Submission deadline: May 4

Call for Case Reports
ACCP affiliate members are invited to submit case reports for presentation during special sessions.
www.acccmeeting.org
Submission deadline: May 4

The CHEST Foundation 2011 Awards Program
The CHEST Foundation tradition of recognizing and rewarding health-care professionals for volunteer service, leadership, and clinical research continues in 2011. You could be eligible for:
• Humanitarian Service Awards
• Distinguished Scholar in Thrombosis Award
• Clinical Research and Leadership Awards
• Scientific Abstract Awards
OneBreath.org
Application deadline: May 4
The State of the College

This is an exciting time to be an ACCP member and even more fulfilling to actively shape ACCP’s future. We invite you to do so …

To: ACCP Members and Other Supporters

From: ACCP Operations Team*

Regarding: The State of the College

Date: February 2011

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A strong financial position.
- The highest impact factor and ranking in the 75-year history of the CHEST journal.
- The largest number of international attendees at the ACCP annual meeting, CHEST 2010.
- Launching OneBreath, a new initiative of The CHEST Foundation, to inspire people to take care of their lungs and heart and never take their next breath for granted.

These are just a few of the many accomplishments that your ACCP achieved this past year. The purpose of this State of the College, which the Operations Team will prepare annually, is to acknowledge and highlight these successes. It is important to note that none of the accomplishments included here would have been remotely possible without the remarkable dedication of our leadership and staff. We profoundly thank ACCP leaders for the considerable time, knowledge, and expertise that they so generously volunteer and ACCP staff for regularly going the “extra mile.”

A series of changes accompanied our successes: some bigger—reengineering the way that the ACCP advocates on behalf of its members and their patients, and some smaller—adopting the Google suite of applications. While change can be difficult, we are resolute in our belief that appropriate changes are essential for the College to stay in the lead in these fast-paced times.

Of course, much work remains to be done. The accomplishments outlined here are first steps in realizing our new vision to be the “global leader in providing education in cardiology, critical care, and sleep medicine to optimize health with patient-centered care.” Read on for a glimpse of some of the exciting plans unfolding at the College. We look forward to working with you to further develop and implement these ideas and continue to advance your ACCP, the authority in clinical chest education.

Operations

Our strategic planning began with the environmental snapshot that leaders and staff took of the College and the subsequent ACCP Strategic Plan 2010–2011. The plan sets ambitious goals that look several years ahead and delineate specific strategies and metrics for measuring our success in achieving these goals. Other crucial documents were reviewed and revised, including the bylaws and conflict-of-interest policy for ACCP leaders. Through our strategic planning, we acknowledged our core competency of providing the best clinical education in chest medicine and realigned staff to reflect this purpose.

Last year, the four ACCP Presidents—President, President-Elect, President-designate, and Immediate Past President—and the Executive Vice President and CEO began working together as a team, including participating in weekly conference calls, to enhance the continuity of leadership for the common purpose of realizing the ACCP strategic plan. The “Four Presidents” at that time were Kalpalatha K. Guntupalli, MD, FCCP; David D. Gutterman, MD, FCCP; Suhail R. Markowski, CAE, and James A. L. Mathers, Jr, MD, FCCP, respectively. The new Four Presidents, including Darcy D. Marciniuk, MD, FCCP, and the EVP/CEO, Paul A. Markowski, CAE, will continue this highly collaborative practice, weaving the themes of each President into the strategic efforts of the College.

Finances

Despite a continued anemic economy, the ACCP maintains a strong financial position. In FY 2009-2010, the ACCP and The CHEST Foundation had total assets of $25,166,791, total liabilities of $8,322,837, and total net assets of $16,843,954. This year, we worked toward a budget surplus of $55,206 before depreciation.

We developed key performance indicators to enhance our budget process and rigorously track our progress in achieving the goals of our strategic plan. The Board of Regents and staff regularly review this statistical snapshot, which includes budget FY 2010-2011, year-to-date actual, along with historical financial, staffing, membership, education, and publications information. Our membership also continues to grow. At the time of this writing, there were 17,956 ACCP members, reflecting a 5% increase since 2008 and a 19% increase (3,440) in total international members.

The ACCP assembled an effective development team that succeeded in securing support for projects that are identified in the ACCP strategic plan. This support is in the form of CME and non-CME grants, as well as other activities that generate non-dues revenue. Given the current external environment that makes it more difficult to obtain funding, this success is achieved by the increased cooperation between our development team and other areas of the College.

Recently, the Development Division and Clinical Education, Informatics, and Resource Development successfully worked together on a non-small cell lung cancer project for 2011-2012, through an ACCP-led collaborative with the American Society for Clinical Pathology, National Thoracic Institute for Quality Improvement and Education, The France Foundation, and CECity. This project offers the ACCP an opportunity to provide knowledge, competency, and performance of interdisciplinary teams that are responsible for the diagnosis, assessment, and personalized care for patients with non-small cell lung cancer.

The Marketing and Public Relations Department has been an integral part of the development and implementation of a COPD project that was funded in 2010. The ACCP-convened COPD Alliance is a campaign to increase awareness of COPD among primary care physicians and is reaching out to thousands of clinicians throughout the United States.

Education Programs

The ACCP hosted the Guidelines International Network (G-I-N) Conference 2010, the first to be held in the United States. The G-I-N Conference brought together record numbers of professionals involved in evidence synthesis, guideline development, implementation, quality improvement, and health policy to integrate knowledge and, ultimately, improve patient care.

We developed and launched the first Pediatric Pulmonary Board Review course and associated e-book study guide in collaboration with the American Academy of Pediatrics (AAP). This first-ever board preparation course in pediatric pulmonology met the increasing education needs of pediatric pulmonologists and, as a result of this joint project, the AAP is working toward the development and implementation of Maintenance of Certification material in 2011.

We developed new models to define the role for and shape of our future education. The Board united with the ACCP Education and the recommendations of the ACCP Advocacy Task Force, which was charged with determining what the ACCP should accomplish with its advocacy efforts and how these efforts should be organized to maximize impact and value to members, patients, and the College. The task force underscored the importance of the ACCP engaging in effective advocacy and called for a targeted and measurable approach.

We collected, reported, and presented data stemming from the work conducted in the interventional and diagnostic bronchoscopy registries. This work enabled the use of aggregated reports, with collaboration from the US Food and Drug Administration, and initiated the facilitation of an ACCP-led bronchoscopy training project, beginning with a fellowship focus, that includes representation from multiple societies, such as the American Thoracic Society, European Respiratory Society, Society for Thoracic Surgeons, British Thoracic Society, Canadian Thoracic Society, American Association for Bronchology and Interventional Pulmonology, and Association of Pulmonary and Critical Care Medicine Program Directors.

Amid the idyllic backdrop of Vancouver, British Columbia, nearly 5,000 attendees descended on CHEST 2010 from October 30 to November 4, 2010, with the largest number of international attendees (30%) in the history of the meeting. CHEST 2010 was noteworthy in other ways. We moved toward “paperless” CHEST meetings by making use of electronic communication tools. The ACCP provided 24/7 access to the most current and late-breaking meeting information and, in so doing, saved considerable printing and paper costs.

New at CHEST 2010, we offered robust online meeting planning tools to allow attendees to search sessions, build a daily itinerary, select sessions that hold interest for them, and shape their day to fit their needs. Attendees could then determine which sessions to attend, and recommend the “can’t miss” meeting for chest physicians.

Communications

We initiated a major overhaul of our information technology infrastructure and Web presence, including the investigation and development of patient education, learning, and management systems, in order to better serve our members. When this process, which typically takes 18 to 24 months, is complete, the resulting new systems will revolutionize the way that the ACCP conducts business.

The CHEST journal recently went mobile with full issues available on the iPhone®, iPad®, and tablet. The College also launched the ACCP board review e-books on the CHEST journal platform to create the www.chestpubs.org site and the first ACCP iPhone®/iPad® app for ACCP SEEK. Last summer, CHEST reached its highest impact factor (6.36) and ranking (3rd out of 43 respiratory journals) (2009 Journal Citation Reports) in its 75-year history, and CHEST Physician has the distinction of being the most read news publication in the pulmonary medicine market (Kantar Media Medical/Surgical Readership Study, December 2010).

We launched two new e-newsletters as part of our ongoing effort to advance communication and transparency. ACCP Communications}

Continued on following page
Continued from previous page

Leadership Update features major initiatives in development at the College, and ACCP NewsBrief is a weekly e-newsletter sent to all ACCP members and includes ACCP/Foundation news, as well as news from the health-care industry.

The CHEST Foundation
The CHEST Foundation had a financially and programmatically successful 2009-2010. The Foundation ended the year with $8,038,904 in total assets and almost $6 million in net assets.

The Foundation launched a new branding campaign, Web site, and public-facing program, OneBreath™, Make The Most of It. Its new Web site at onebreath.org captures its mission, using the three pillars of education, care, and community, and is providing a breadth of new resources to ACCP members, their patients, and the public.

The Foundation continued its efforts with its strategic partners through the Patient Safety Collaborative (PSC). The collaborative created a white paper on surgical site infection, developed an online tool kit, and planned a pilot project focusing on carefully selected and limited geographic regions—the Middle East, Latin America, India, and China—with significant potential.

We also will reassess our communications, with an emphasis on social media, and continue the revamping of our information technology infrastructure and Web presence. Overseeing these and other changes will demand effective leadership, which is why the ACCP will implement an annual Board self-assessment tool and redouble our commitment to leadership development at all levels of member engagement.

The College is first and foremost a membership organization. Consequently, it is imperative that members like you be actively involved. This is an exciting time to be an ACCP member and even more fulfilling to actively shape ACCP’s future. We invite you to do so by answering the call for nominations this spring or simply by posting a comment to one of our blogs. Your participation at any level is welcome.

On behalf of the entire ACCP staff, thank you for the honor and pleasure of serving you, your patients, and your ACCP.

*The ACCP Operations Team includes the following staff: Paul A. Markowski, CAE, Executive Vice President and CEO; P. Stratton Davies, CPA, Senior Vice President and Chief Financial Officer; Ed Dellert, RN, MBA, CCMP, Senior Vice President, Clinical Education, Informatics, and Research; Dave Eubanks, EdD, RRT, FCCP(Hon), Senior Vice President, Business and Development; Marilyn Ledere, CPA, Executive Director, The CHEST Foundation; William Rizer, SPHR, CCP, Human Resources Director; Stacy Seiden, MPP, Special Projects Manager; and Stephen Welch, Senior Vice President, Communications.

To enhance communication between ACCP leaders and members, the ACCP Presidents have launched a new blog, From the Presidents. The inaugural post by ACCP President, Dr. David D. Guterman, FCCP, explains the vision and goals of the blog and features Dr. Guterman’s call for you to share your ACCP experiences.

From the Presidents will feature regular blogs about the College, medical and health-care issues, the profession, and other member-related topics of interest. In addition to Dr. Guterman, Dr. Suhasi Raoof, FCCP, ACCP President-Elect; Dr. Darcy D. Marciniak, FCCP, ACCP President-Designate; and Dr. Kalpalatha K. Guntupalli, FCCP, ACCP Immediate Past President, will contribute to the blog.

Here’s your chance—post your comments today!

You can view the inaugural blog and add your comments at www.chestnet.org/accp/blogs/introducing-presidents-new-accp-blog.

AMERICAN COLLEGE OF CHEST PHYSICIANS

**2011 Education Calendar**

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<tr>
<th>Event</th>
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<tr>
<td>Celebration of Pediatric Pulmonology</td>
<td>April 8-10</td>
<td>Ft. Lauderdale, FL</td>
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<tr>
<td>ACCP Critical Care Medicine Board Review</td>
<td>August 26-30</td>
<td>San Antonio, TX</td>
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<tr>
<td>ACCP Sleep Medicine Board Review</td>
<td>August 26-29</td>
<td>San Antonio, TX</td>
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<tr>
<td>Lung Pathology 2011</td>
<td>August 30</td>
<td>San Antonio, TX</td>
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<tr>
<td>Mechanical Ventilation 2011</td>
<td>August 30</td>
<td>San Antonio, TX</td>
</tr>
<tr>
<td>ABIM Critical Care Medicine and Pulmonary Disease SEP Modules</td>
<td>August 30</td>
<td>San Antonio, TX</td>
</tr>
<tr>
<td>ACCP Pulmonary Medicine Board Review</td>
<td>August 31-September 4</td>
<td>San Antonio, TX</td>
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<tr>
<td>CHEST 2011</td>
<td>October 22-26</td>
<td>Honolulu, Hawaii</td>
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**ACCP Simulation Program for Advanced Clinical Education**

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<tr>
<th>Program</th>
<th>Dates</th>
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<tr>
<td>Mechanical Ventilation</td>
<td>February 25-27</td>
<td>Chicago, IL</td>
</tr>
<tr>
<td>Basic and Advanced Bronchoscopy Skills</td>
<td>August 5-7</td>
<td>Chicago, IL</td>
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<tr>
<td>Difficult Airway Management</td>
<td>March 18-20</td>
<td>Chicago, IL</td>
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<tr>
<td>Focused Pleural and Vascular Ultrasound</td>
<td>September 22-23</td>
<td>Chicago, IL</td>
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<tr>
<td>Ultrasonography: Fundamentals in Critical Care</td>
<td>April 15-17</td>
<td>Baltimore, MD</td>
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<tr>
<td>Critical Care Echocardiography</td>
<td>September 24-25</td>
<td>Chicago, IL</td>
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www.chestnet.org/accp/events
(800) 343-2227 or +1 (847) 498-1400
The concept of venous interruption can be traced back to Armand Trousseau’s lectures at the Hotel Dieu in Paris in the mid-19th century (Trousseau A. Phlegmasia alba dolens. In: Trousseau A, ed. Clinique Medicale de l’Hotel-Dieu de Paris. Paris, France: Balliere, 1865; 654). Although surgical venous interruption was occasionally performed, its invasive nature and attendant morbidity and mortality prevented widespread application. This situation dramatically changed with the introduction of the stainless steel Greenfield filter in 1973, which made percutaneous venous interruption feasible (Greenfield et al. Surgery. 1973;73(4):599). Between 1979 and 1999, the number of vena cava filters (VCF) placed annually in the United States rose 25-fold, from 2,000 to 49,000 (Stein et al. Arch Intern Med. 2004;164(1):1541). With the introduction of optional/retrievable VCF that are easy to insert, the expansion in clinical use of these devices has continued to increase. In 2007, nearly 167,000 VCF were placed in the United States, and it is estimated that annual use will top 259,000 in 2012. This expansion in VCF use has been largely driven by the increasing availability of optional filters and increased use for prophylactic rather than treatment indications (Smouse and Jocab. Endovascular Today. 2010;74-77; Athanassiou et al. Radiology. 2009;216(1):154; Kim et al. J Vasc Interv Radiol. 2008;19(3):393). Despite the popularity of these devices, there is surprisingly little scholarship documenting their efficacy. Among 2,503 publications on VCF, only two randomized controlled trials (RCT) have been conducted examining outcomes. In comparison, 252 RCTs have been reported for the use of low-molecular-weight heparin for venous thromboembolism (VTE) among 2,265 publications (PubMed search conducted Nov 14, 2010).

Consequently, the appropriate indications for VCF insertion continue to be a subject of considerable debate, in large part due to the limited evidence supporting their utility in the treatment of VTE (Table 1). There is broad support for their application in patients who have acute VTE and contraindications to anticoagulation. Although it did not test the efficacy of VCF in the absence of anticoagulation, the PREPIC study did show that filters reduce the incidence of pulmonary embolism (PE) by 63% (6.2% vs 15.1%; hazard ratio 0.37 [95% CI 0.17-0.79]; P = 0.08) in patients who received at least 3 months of anticoagulation therapy (PREPIC Study Group. Circulation. 2005;112(3):416). However, skeptics are much less likely to support filter insertion for other indications, such as failure of anticoagulation, as these patients were excluded from participation in PREPIC (Decousus et al. N Engl J Med. 1998;338(7):409). In these instances, hematologists are more apt to intensify or alter anticoagulant therapy (eg, increase the target INR or switch to an alternative anticoagulant, such as a low-molecular-weight heparin), and look for a potentially correctable etiology for anticoagulation failure (eg, heparin-induced thrombocytopenia, antiphospholipid syndrome, Trousseau syndrome, vascular compression—May-Thurner syndrome, thoracic outlet syndrome, and others), rather than resort to filter placement. In many instances, a VCF may impart adequate risks than enhance local thrombotic control by reducing blood flow proximal to the site of thrombosis. Patients with cancer and idiopathic VTE appear to be at particularly high risk for filter-associated thrombotic complications (PREPIC Study Group. Circulation. 2005;112(3):416).

Although vena cava filters have traditionally been placed in the inferior vena cava (IVC), several recently published papers have examined filter placement in the superior vena cava (SVC) (Usos et al. Ann Vasc Surg. 2009;23(2):350). White et al (2005) have emphasized that SVC filters require placement of a filter through the upper extremity and SVC, the incidence is significantly less than the IVC (Muñoz et al and the RIETE Investigators. Chest. 2008;133(1):143). In addition, the complications of filters in the SVC location can be devastating (Owens et al. J Vasc Interv Radiol. 2010;21(6):779). Placement of filters in the IVC should be considered only in extremisating circumstances.


In addition to concerns about the limited data documenting the effectiveness of filters for many of their indications, there are legitimate reasons to be concerned about the safety profile of VCF. While fatal periprocedural complications are rare (0.12%) (Athanassiou et al. Radiology. 2000;216(1):54), deep venous thrombosis (35.7% vs 27.5%, HR 1.52 [95% CI 1.02-2.27]; P = 0.042) and IVC thrombosis (13% vs 1%), these two patients received IVC filters during follow-up are common adverse events associated with filter placement (PREPIC Study Group. Circulation. 2005;112(3):416). Although previous reports have suggested that migration and mechanical failures are infrequent events after filter placement (Hann and Streiff. Blood Rev. 2015;19(4):179; Owens et al. J Vasc Interv Radiol. 2010;21(6):779; Athanassiou et al. Radiology. 2000;216(1):54), a recent study indicates that this conclusion may need to be revised. Nicholson and colleagues conducted a radiographic surveillance study of strut fracture in 80 controls and Bard G2 filters (Bard Peripheral Vascular, Tempe AZ) at their institution (Nicholson et al. Arch Intern Med. 2010;170(20):1827). They noted a high rate of filter leg fracture for both devices (13/40, 16%), seven of 28 (25%) Recovery filters and 6 of 52 (12%) G2 filters suffered strut fracture. In seven patients, these fractures were associated with clinical symptoms, including one sudden death and one episode of cardiac tamponade due to a hemorrhagic pericardial effusion that required emergent cardiac surgery (Nicholson et al. Arch Intern Med. 2010;170(20):1827). Thus, we are left with a number of questions. Given the risks of thromboembolism posed by the presence of a filter, should all patients with IVC filters receive indefinite anticoagulation? The answer to this question is of significant clinical importance, since the vast majority of optional/retrievable filters remains unretrieved (Mission et al. J Gen Intern Med. 2010;25(4):321; Dabbagh et al. Thromb Res. 2010;126(5):693), and many are placed for controversial or questionable indications (Spencer et al. Arch Intern Med. 2010;170(16):1456). Are the problems noted by Nicholson and colleagues a result of selected bias, or do they represent the tip of a previously unrecognized iceberg? Is this complication unique to the Bard Recovery and Bard G2 filters, or is this experience generalizable to all filters? Are optional/retrievable filters more susceptible to mechanical failures than permanent filter models as a consequence of their design? These and many other outstanding questions and concerns regarding VCF warrant further rigorous investigation. In some instances (eg, PE prevention in trauma patients), randomized controlled trials are feasible, while in other circumstances (eg, complications of VCF), prospective cohort studies are a more realistic approach. The important goal is to increase the number and quality of clinical studies of VCF.

Two years ago, the surgeon general, Admiral Steven Galston, MD, issued a call to action to improve efforts on prevention of VTE (www.surgeongeneral.gov/topics/deepven). Accessed Jan 20, 2011). In this spirit, we believe these recent studies sound a clarion call to action to intensively study VCF to better assess their benefits and risks. They represent a valuable tool in the treatment of VTE, but further information is needed as to when and in whom we should use these devices and what are the short- and long-term complications of their use. We think this research will need to be sponsored and supported at the federal level, as there is little incentive for individual manufacturers to conduct these studies. Although almost 40 years have passed since the introduction of the stainless steel Greenfield filter, many questions remain about the safety and efficacy of these devices. The report of Nicholson and colleagues indicates that a careful reexamination of our clinical use of VCF is urgently needed.

Michael B. Streiff, MD
Division of Hematology, Department of Medicine
Johns Hopkins Medical Institutions
Baltimore, MD

Kevin Kim, MD
Division of Interventional Radiology and Image Guided Medicine
Department of Radiology
Emory University, Atlanta, GA

Kevin Hong, MD
Division of Vascular and Interventional Radiology, Department of Radiology
Johns Hopkins Medical Institutions
Baltimore, MD

Indications for Vena Cava Filters

Broad Agreement
Acute VTE with contraindication to anticoagulation

Less Agreement
Failure of anticoagulation
Chronic thromboembolic pulmonary hypertension
Limited cardiopulmonary reserve and acute VTE
Iliac vein thrombosis
Proximal free-floating thrombus
Thrombolysis of iliacal DVT
Treatment of VTE in cancer patients
Treatment of VTE in pregnant patients
VTE prophylaxis in high-risk trauma patients
VTE prophylaxis in high-risk surgery patients
FEBRUARY 2011 • CHEST PHYSICIAN NEWS FROM THE COLLEGE

BY ROBERT DEMARCO, MD, FCCP, CHAIR; AND DONNA KNAPP BYBEE, FACMP, VICE-CHAIR

The Practice Management Committee (PMC), a standing committee of the ACCP, meets regularly to discuss issues related to the business of medicine, as well as proper coding and reimbursement for pulmonary, critical care, and sleep medicine physician practices. In addition to working with the Centers for Medicare & Medicaid Services (CMS) and the AMA/CPT Editorial Panel and the Speciality Society Relative Value Scale Update Committee (RUC) on the development of new CPT codes and the establishment of appropriate physician work values, the ACCP PMC monitors and comments on legislative and regulatory policies relevant to the practice of pulmonary, critical care, and sleep medicine. On December 28, 2010, CMS announced the new CY 2011 Medicare Physician Fee Schedule conversion factor to be $33.9764. The revised conversion factor, effective January 1, 2011, represents a 7.86% reduction from the FY 2010 conversion factor of $36.8729.

The ACCP PMC has been working diligently to analyze the impact of the freeze of the sustainable growth rate (SGR), as well as other changes that CMS has made to physician reimbursement on codes of interest to pulmonary, critical care, and sleep physicians. The SGR freeze was enacted through the Medicare and Medicaid Extenders Act (MMEA) on December 15, 2010, to provide a 0% update (as opposed to the 25% proposed cut) to the Medicare Physician Fee Schedule for claims of services rendered between January 1, 2011, and December 31, 2011. Although the physician fee schedule update will be 0%, changes have been made to the Medicare Economic Index, which was rebased from $134.95 in 2010 to $137.60 in 2011. The decrease in the CY 2011 conversion factor, therefore, negated some of these other reimbursement formula increases. CMS provided the information to contractors to implement the final rule in CMS Transmittal 828, available at www.cms.gov/transmittals/downloads/R520TN.pdf. Overall, these changes result in a 1% loss in reimbursement to the pulmonary community for 2011. The ACCP PMC will continue to work on behalf of its members.

We fully expect cuts to the sleep codes, and today expected the cuts to be greater. For CY 2011, CMS rebased the Medicare Economic Index (MEI) from CY 2000 to 2006, which increased some of the practice expense (PE) and the malpractice relative value units. Sleep physicians were surveyed, and the data were analyzed by the sleep societies, which presented the data to the RUC. A consensus panel of ACCP/ATS/AAN/AASM members concluded the review of the PE inputs for clinical labor, medical supplies, and equipment attributable to each code that was reviewed by the RUC PE subcommittee, and inputs were forwarded to CMS, which made the final decision on RVUs for physician work, PE, and malpractice. The reason for the decreases (and because CMS transitions PE RVUs for existing codes over 4 years, we expect future PE decreases to the existing sleep codes, not to the two new unattended sleep codes, 95800 and 95801) is because of the economies of scale with performing sleep studies now, compared with the time when the CPT codes were introduced and valued. In other words, sleep technicians are now doing two patients, instead of one, and the analysis of sleep studies is now automated, also saving time. With so decreasing times, these are the resulting values.

The AMA provides an example of the CMS final rule on CPT 99214 that has a 1.34% increase for 2011 (www.ama-assn.org/ama/pub/upload/mm/399/2011-medicare-phys-payment-rates.pdf). Of importance to pulmonary care in the office/outpatient setting are the increases in CPT for sleep medicine, from $999.93 in 2010 to $102.27 in 2011 and the 2% increase to 99215 from $317.60 in 2010 to $317.60 in 2011. These are nationalized payment amounts. Each practice changes that to its regional adjustment factor.

Offsetting increases may balance out the negative impact to sleep physicians. The newest edition of Coding for Chest Medicine 2011 is available for purchase at www.chestnet.org.

If you have any questions or concerns, please contact Marla Brichta, ACCP Manager, Health Care Practice and Reimbursement, at mbrichta@chestnet.org.

### Alvin Lever Honored by AACN

The American Association of Critical-Care Nurses (AACN) awarded Alvin Lever, MA, FCCP (Hon.), the Marguerite Rodgers Kinney Award for Distinguished Career during its 2010 National Teaching Institute & Critical Care Exposition in Washington, DC. Mr. Lever, the immediate past Executive Vice President and CEO of the ACCP—an important AACN partner—received this Visionary Leadership Award for extraordinary and distinguished career contributions to the AACN mission and vision.

Mr. Lever’s creativity and vision led to strategic technology development initiatives at the ACCP that expanded key alliances, leveraged resources effectively, and created new markets, programs, and products. Customization, integration, centralization, and business focus helped to achieve these goals. Established in 1997 and rebranded in 2008, the AACN-CCP online has grown from $1,000 g to the charity of their choice, lifetime membership in AACN, and a crystal replica of the presidential “Vision” icon.

### OneBreath.org Now Available

The CHEST Foundation’s public education initiative, OneBreath™: Make The Most Of It, integrates The Foundation’s programs with the education mission of the ACCP. Living well means breathing well, and OneBreath.org will promote access to prevention tools, tips, and community-based activities that will inspire members, patients, and the public to take care of their lung and heart health.

Traditional CHEST Foundation programs are featured under the pillars of education, care, and community. We invite you to visit OneBreath.org to log in and become an online community member. You can use your ACCP ID as your password to simplify your ACCP online accounts. When you become an online community member, you will have a more personal experience through features that allow you to:

- Update your profile.
- View your giving history.
- Check pledge or recurring gift status.
- Manage your online subscriptions.
- Search the Directory for your ACCP colleagues’ contact information.
- Send an e-card when you donate online. These colorful cards are taken from the Love Your Lungs® poster contest winners and promote tobacco prevention.

Let us know your point of view by participating in online polls and surveys. Coming soon, watch for our quarterly newsletter, EXTRAORDINAIR, as well as a blog, discussion board, and document sharing. Visit OneBreath.org today and support our efforts to expand our reach and promote positive health habits and activities for better lung and heart health for everyone.

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### Conversion Factor

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Note: 2010 conversion factor was $36.8729; 2011 conversion factor is $33.9764.
The CHEST Foundation Awards Program 2011

The clinical research awards reflect the ACCP’s multidisciplinary nature. Alpha-1 Foundation and The CHEST Foundation Clinical Research Award in COPD and Alpha-1 Antitrypsin (AAT) Deficiency. This 1-year $25,000 award supports research focused on COPD and AAT deficiency. Research projects primarily in usual COPD (not associated with AAT deficiency) are allowed. Projects with a focus on AAT deficiency are encouraged. The CHEST Foundation and the Respiratory Health Association of Metropolitan Chicago Clinical Research Award in Women’s Lung Health. This 1-year $10,000 award supports a clinical research project related to women’s lung health, which may include research on gender differences in various lung diseases, such as COPD and lung cancer.

Association of Specialty Professors and The CHEST Foundation of the ACCP Geriatric Development Award. This 2-year $50,000 award supports the career development of junior faculty in the early stages of their research career in geriatrics. To be eligible for this award, you must have first applied for the GEMSSTAR award through the National Institute on Aging and received a fundable score. The deadline to apply for the GEMSSTAR award was Nov 3, 2010.

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The CHEST Foundation continues its support of leadership in end-of-life care through the Roger C. Bone Advancements in End-of-Life Care Award. This 1-year award of $10,000 supports an ACCP member’s project that stresses the importance of communication, compassion, and effective listening. The award is given for leadership in end-of-life care—on the international, national, or local level—and does not fund research or provide seed money for new programs or projects.

The D. Robert McCaffree, MD, Master FCCP Humanitarian Awards support the volunteer efforts of those who give time and expertise to improve the health of communities around the world. The award provides funds to nonprofit and governmental organizations where ACCP members provide pro bono service. The CHEST Foundation will grant awards in amounts of $5,000 and up to $15,000, to a total of $90,000 in 2011. The CHEST Foundation Awards Committee encourages ACCP members to take advantage of this important member benefit by applying for an award. Learn more and apply for an award at OneBreath.org. The deadline for all awards is May 4, 2011.

The CHEST Foundation provides funds for volunteer service, leadership, and clinical research throughout its annual awards program. In 2011, awards are offered in thrombosis, end-of-life care, women’s health, geriatrics, COPD, lung cancer, and humanitarian service. The CHEST Foundation offers 1-, 2-, and 3-year awards to ACCP members’ projects that meet the qualifications.

The Third GlaxoSmithKline Distinguished Scholar in Thrombosis award is open to ACCP members who are FCCPs. It supports clinical educational projects to improve patient care and is intended for the investigation of issues that are not easily supported through traditional funding. The award grants $150,000 over the course of 3 years to support an ACCP Fellow’s thrombosis-related project and/or service that does one or more of the following:

- Investigates alternatives for treatment
- Educates patients about options for diagnosis and treatment
- Disseminates new knowledge about diagnosis and treatment
- Addresses family, legislative, or regulatory issues
- Defines new mechanisms leading to innovations and improvements in treatment.

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Humanitarianism in Haiti

A year after the earthquake in Haiti, health-care providers continue to volunteer in an attempt to fill our Caribbean neighbor’s medical void. In recent years, several domestic and international natural disasters have captured the attention of the medical community and the public at large. Yet, the Haitian crisis seems to have received more United States–based medical “help” for multiple reasons, such as the proximity between the two nations; 200 years of cultural connections; longstanding American medical projects in Haiti; the enormity of the disaster; and, most importantly, the dire need of the Haitian people.

The complexities of going into a disaster zone and working in a country with a weak public health system are numerous and need to be examined critically. International nongovernmental organizations (NGOs) and Haitian health-care providers on the ground mobilized immediately after the disaster. They were joined by an avalanche of good samaritans from a geographically diverse group of hospitals, American NGOs, and communities started through social-networking sites like Facebook. The response created a unique dynamic in Jimini, a dusty city in the Dominican Republic that borders Haiti. At the public hospital in Jimini, Dominican physicians worked tirelessly, treating crush injuries in patients flown and driven in from Port-au-Prince. Up the road, at Good Samaritan Hospital, an international crew of health-care providers organized themselves to provide care. Admirably, the outpatient surgical center cared for hundreds of patients and housed volunteers, assisted by an NGO deployed to run the center prior to the storm.

Despite the valiant efforts, there were a few glitches. There were abundant concerns about professionalism. While awaiting helicopter transfer of patients to hospitals in larger Dominican cities, transporters could be found videotaping the process with smartphones while holding stretchers. Some critically ill patients were transferred to facilities too overburdened and understaffed to care for them. Poor coordination occasionally exacerbated the chaos and frenzy of activity. In one instance, an American military helicopter was called to pick up a pediatric patient not authorized to be picked up. The patient’s father was devastated that his critically ill son was not going to the American medical ship, and the helicopter made an unnecessary landing at Good Samaritan.

Reaction to the crisis has highlighted the need to increase resources in Haiti and the Dominican Republic to handle disasters and care for the critically ill or injured. Disaster training and preparation should enhance the response and relief effort; untrained volunteers can participate in disaster relief but should not direct it. Interested individuals may consider taking a Fundamentals of Disaster Management course (www.sccm.org/FCCS_and_Training_Courses/FD/M/Pages/default.aspx) or receive advanced training in emergency management. These potential pitfalls were well anticipated by the Israeli military in its disaster response. It recognized that ethical dilemmas would exist for the team in Haiti, due to the limited resources. Therefore, it created an ad hoc ethics committee and a realistic triage system to support its staff in making treatment decisions (Merin et al. N Engl J Med. 2010;362(11):e38). Today, limitations persist beyond the disaster’s acute phase. Field hospitals run by foreign health-care providers remain, and medical decisions are made daily by individuals who do not normally practice in resource-limited environments, a learning experience for foreign health-care providers and an unnecessarily traumatic one for patients and physicians.

The war in Iraq provides a relevant example of alternative management systems. Cannon and Smith described providing care for critically ill Iraqi pediatric trauma patients and inadvertently winning the “hearts and minds” of the local people around their base in Balad. The airmen intervened because a lack of facilities led them to a 70% mortality rate for critically ill patients. Their experience led them to suggest a “landmark” partnership between NGOs and the military to supplement the Iraqi medical system (Cannon and Smith. Crit Care Med. 2009;37:2322). The contrast between providing medical care in the Iraqi war effort vs the Haitian humanitarian effort is immense, but there is one important similarity. The military presence, in both situations, substantially improved medical care. Amundson and colleagues described their experience on the hospital ship USNS COMFORT in Haiti where they took care of a diverse group of patients, including the critically ill (Amundson et al. Ann Intern Med. 2010;152(11):733). The USNS COMFORT initially partnered with Project Hope to allow civilian medical personnel aboard. After the ship left, however, the American military had a much more limited partnership with the medical relief effort. NGOs continued to run busy field hospitals, and the military provided supplies, occasional personnel, and technical advice, as able. The lack of an ongoing formal partnership with the military led to a loss of expertise that could have benefited the continuing relief effort. It is our personal belief that the military staying formally involved in the medical process in Haiti could have increased our overall ability to serve our Haitian patients. Yet, not all situations are similar. Many times, it may not be feasible or even in an NGO’s best interest to work with the military, but it should be considered.

After the acute and subacute phases of a disaster situation, the most important way to continue to improve medical care is to engage a local resource. In the long term, local organizations understand how to deliver more effective health care to their own populace. Long before the world focused on earthquake-ravaged Haiti, a community center in Petit Gaque, a small city 2 hours outside of Port-au-Prince, provided health care to its local residents in recent years. The Henri Gerard Desgranges Foundation (HGD, hgdfoundation.wordpress.com) has struggled to reopen its school and health clinic after the disaster due to a lack of funding and medical staff. The foundation’s lab was destroyed, and fewer Haitian physicians are present, but the patients remain. Between 50 and 200 patients a day are seen at HGD, with specific days focused on obstetrics and pediatrics. The center has had volunteers from the US, Canada, and France rotating in for 1-week to 2-month stints. The contribution of foreigners is commendable, but the clinic’s future depends on the ability of Haitian physicians to resume management.

Medical providers who wish to volunteer in Haiti should evaluate whether their money, time, and effort would be better spent in helping existing Haitian resources rebuild rather than going on week-long volunteer missions. A moment of reflection on the personal motivation for a medical mission may profoundly impact the choice to go to a disaster zone. Haitians need our “help,” but we must be more discriminating in how we extend our helping hands.

Dr. Nitin Puri Cooper Hospital Robert Wood Johnson University of Medicine and Dentistry of New Jersey Camden, NJ
Lt. Col. Terence Lemengan, USAF, MC, Emergency Medicine Staff Physician Wilford Hall Medical Center Lackland AFB, San Antonio, TX

The opinions expressed are those of the authors and not those of the Department of Defense or the US Air Force.

Dr. Marilyn G. Foreman, FCCP Editor, Pulmonary Perspectives Dr. Loren J. Harris, FCCP Deputy Editor, Pulmonary Perspectives

T he recent cholera epidemic brings the fragility of the medical-care system in Haiti and the needs of the Haitian people, in the earthquake’s aftermath, back into stark focus. This commentary is a partial reflection of the experiences of the authors. Dr. Puri, an ACCP Affiliate, has traveled to Haiti four times. Dr. Lemengan has also made multiple trips to Haiti, the poorest country in North America. CAPT Dennis Amundson, MC, USN, FCCP, whose work is referenced in this article, is the chair of the ACCP Disaster Response Network. We are proud of the humanitarian contributions of our ACCP members and agree that long-term solutions for medical care in Haiti require the input of Haitians and should emphasize sustainability.

—Dr. Marilyn G. Foreman, FCCP
Study Shows Rivaroxaban Valid for VTE Prophylaxis

BY NEIL OSTERWEIL
Elsevier Global Medical News

ORLANDO – The investigational oral anticoagulant rivaroxaban was not inferior to a combination of the low-molecular-weight heparin enoxaparin and a vitamin K antagonist for reducing risk of recurrent deep venous thromboembolism for up to 1 year, reported investigators with the EINSTEIN Acute DVT study.

The EINSTEIN Acute DVT trial compared oral rivaroxaban alone with enoxaparin followed by a vitamin K antagonist for prophylaxis of recurrent VTE or pulmonary embolism in 3,449 patients. Patients received oral rivaroxaban 15 mg twice daily for 3 weeks, followed by 20 mg once daily for 3, 6, or 12 months, said Dr. Harry R. Büller at the annual meeting of the American Society of Hematology.

The EINSTEIN-extension study compared rivaroxaban with placebo in 1,197 patients who had completed 6–12 months of rivaroxaban in the EINSTEIN studies or 6–12 months of a vitamin K antagonist, either in the EINSTEIN studies or in routine care. The primary efficacy end point for both studies was the incidence of recurrent VTE. The primary safety outcome for the acute DVT trial was major bleeding or clinically relevant minor bleeding. The major safety outcome in the extension trial was major bleeding (N. Engl. J. Med. 2010;363:2499-510).

Incidence of major bleeding or clinically relevant nonmajor bleeding was identical in the two groups, at 8.1%. Additionally, rivaroxaban, a factor Xa inhibitor in late-stage clinical development, was superior in efficacy to placebo in a randomized double-blind extension study. VTE or pulmonary embolism occurred in 2.1% of 1,731 patients randomized to rivaroxaban and in 3.3% of 1,718 patients randomized to enoxaparin (Lovenox) followed by either warfarin or acenocoumarol.

In the acute trial, there were 36 VTE events in the rivaroxaban group, compared with 51 in the enoxaparin/vitamin K antagonist group (hazard ratio, 0.68; P less than .001). In each group, 8.1% of patients had a recurrent VTE.

In the continuation trial, 8 events occurred in 602 patients (1.3%) treated with rivaroxaban, compared with 42 of 594 (7.1%) treated with the enoxaparin/vitamin K antagonist regimen (HR, 0.18; P less than .001). Four major bleeding events occurred in patients treated with rivaroxaban vs. none in those who received placebo.

“This regimen of 15 mg [rivaroxaban] twice a day for the first 3 weeks followed by 20 mg for the remainder period provides clinicians and patients, I think, with an attractive and simple treatment option for venous thrombosis,” Dr. Büller of the Academic Medical Center in Amsterdam, the Netherlands, said in a press briefing.

Risk Score May Predict Recurrent VTE in Cancer

BY NEIL OSTERWEIL
Elsevier Global Medical News

ORLANDO – Among patients with cancer-associated thrombosis, women and those with lung cancer or a history of at least one venous thromboembolic event are at significantly increased risk for recurrent emboli and may require prophylaxis with low-molecular-weight heparin or more aggressive anticoagulation, reported investigators who have reported.

In contrast, patients with stage I malignancies or breast cancer are at relatively low risk for venous thromboembolism (VTE) recurrence and may need only a vitamin K antagonist such as warfarin to prevent a second event, Dr. Martha L. Louzada said at a press briefing in advance of a presentation at the annual meeting of the American Society of Hematology.

The investigators used the data from a retrospective chart study to develop a risk score for determining the clinical probability of VTE recurrence. Each independent predictor variable received a point score relative to the magnitude of risk it imposes. Patients with a score from 3 to 0 are deemed to be at low risk (4.5% chance of recurrence), whereas those with scores from 1 to 3 are considered to be at high risk (19.7% chance of recurrence). They were able to reproduce the rule by applying it to data from two randomized controlled trials that compared a low-molecular-weight heparin with a vitamin K antagonist.

“Our future goal is to prospectively validate this clinical prediction rule to assess further reproducibility and generalizability,” Dr. Louzada of the University of Western Ontario in London said at the briefing.

To determine whether VTE prophylaxis strategies should be tailored to meet individual patient characteristics or cancer types, the investigators took a retrospective look at the charts of 543 patients with cancer and VTE who were followed at the thrombosis unit of the Ottawa Hospital from 2002 through 2004 and from 2007 through 2008. The investigators restricted their analysis to those patients who had recurrent VTE within 6 months of ongoing anticoagulation therapy. They conducted a univariate analysis to gauge the strength of the association between each potential risk factor and VTE recurrence, and evaluated all likely risk-predictor candidates in a logistic regression model.

In all, 55 patients (10.1%) had a recurrent VTE, but the rates of recurrence were similar between the groups, suggesting that treatment type did not have an effect (recurrence rate 9.3% for vitamin K antagonists, 10.5% for low-molecular-weight heparin).

In the multivariate analysis, the authors identified as significant predictors of an increased risk, lung cancer (odds ratio 2.55), a history of prior VTE (OR 2.42), and female gender (OR 1.82). Predictors for decreased risk were stage I malignancies (OR 0.97) and breast cancer (OR 0.46).

“The patient even with breast cancer can have a high risk, because the majority of patients are females and being female is a high-risk predictor, whereas breast cancer in a low-risk, so it’s going to depend on the stage of malignancy of the patient and also whether the patient has a previous history of venous thrombosis,” she said.

The study was internally funded. Dr. Louzada said she had no relevant financial disclosures.
Having a parent who smoked increased the likelihood of high BP by 21%.

Although the effects of active and passive tobacco exposure on cardiovascular functions in adults are well known and have been widely demonstrated, the ef-
facts of passive tobacco smoke exposure on childhood blood pressure have not been reported previously.

Of note, maternal— but not paternal—cigarette consumption had a quantita-
tive relationship with childhood blood pressure, which may be a

Table 1. Incidence (%) of Adverse Reactions Through Use of Care Reported in 26% of Patients Undergoing CPR

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

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<td>Septic Shock</td>
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</tr>
<tr>
<td>Diabetes</td>
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<tr>
<td>Bacterial Endocarditis</td>
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<tr>
<td>Kaposi Sarcoma</td>
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</tr>
<tr>
<td>Tuberculosis</td>
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<tr>
<td>AIDS</td>
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<td>0</td>
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<tr>
<td>Other</td>
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Table 3. Assay Results for Adverse Reactions

<table>
<thead>
<tr>
<th>Assay</th>
<th>TYGACIL (n=144)</th>
<th>Comparator (n=126)</th>
<th>Comparator% (n=126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Infection</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Rash</td>
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</tbody>
</table>

Table 4. Comparison of TYGACIL and Comparator for Overall Survival Rate

<table>
<thead>
<tr>
<th>Survival Rate</th>
<th>TYGACIL (n=144)</th>
<th>Comparator (n=126)</th>
<th>Comparator% (n=126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Infection</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Rash</td>
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</tbody>
</table>

Table 5. Comparison of TYGACIL and Comparator for Mortality Rate

<table>
<thead>
<tr>
<th>Mortality Rate</th>
<th>TYGACIL (n=144)</th>
<th>Comparator (n=126)</th>
<th>Comparator% (n=126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Infection</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Rash</td>
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<td>3</td>
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</tbody>
</table>

Table 6. Comparison of TYGACIL and Comparator for Hospital Admission Rate

<table>
<thead>
<tr>
<th>Hospital Admission Rate</th>
<th>TYGACIL (n=144)</th>
<th>Comparator (n=126)</th>
<th>Comparator% (n=126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
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<td>3</td>
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</tr>
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<td>Infection</td>
<td>3</td>
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</tr>
<tr>
<td>Rash</td>
<td>3</td>
<td>3</td>
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</tr>
</tbody>
</table>

Table 7. Comparison of TYGACIL and Comparator for Blood Pressure

<table>
<thead>
<tr>
<th>Blood Pressure</th>
<th>TYGACIL (n=144)</th>
<th>Comparator (n=126)</th>
<th>Comparator% (n=126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>3</td>
<td>3</td>
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<td>Diarrhea</td>
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<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Infection</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Rash</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 8. Comparison of TYGACIL and Comparator for Heart Rate

<table>
<thead>
<tr>
<th>Heart Rate</th>
<th>TYGACIL (n=144)</th>
<th>Comparator (n=126)</th>
<th>Comparator% (n=126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Nausea</td>
<td>3</td>
<td>3</td>
<td>3</td>
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<td>Diarrhea</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
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<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Rash</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>
**TYGACIL is in the 2009 IDSA/SIS guidelines for cIAI and the 2009 SIS guidelines for cSSSI.**

**Expanded broad-spectrum coverage**

**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*.
- **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.
- The safety and effectiveness of **TYGACIL** in patients below age 18 and lactating women have not been established.

**References:**
3. **TYGACIL®** (tigecycline) Prescribing Information, Wyeth Pharmaceuticals Inc.