Late Stage of Sepsis May Hold Treatment Option

Evidence found for immunosuppression.

BY MARY ANN MOON
Elsevier Global Medical News

During the natural course of sepsis, patients enter an immunosuppressed state after the initial intense inflammatory response well known to clinicians as a “cytokine storm.”

Most therapies for sepsis target this initial hyperinflammatory state and are focused on blocking inflammation and immune activation. Such therapies may be successful if used early in the course of sepsis, but harmful if used during the later, underrecognized immunosuppressed phase, said Jonathan S. Boomer, Ph.D., of the department of medicine, Washington University, St. Louis, and his associates.

This latter phase of sepsis only came to light once clinical management improved enough to allow these patients to survive the early hyperinflammatory phase. Then clinicians began noting that patients who survived early sepsis often developed nosocomial infections with organisms that typically do not affect immunocompetent hosts. These patients also frequently experienced reactivation of latent viruses, Dr. Boomer and his colleagues wrote in JAMA.

These observations lead some to hypothesize that hyperinflammation gives way to significant immunosuppression in such patients. The hypothesis has been controversial. Dr. Boomer and his associates explored the issue through rapid postmortem examination of cells from the spleens and lungs of affected patients — “a lymphoid organ and a peripheral organ that are frequent sites of nosocomial infection.”

See Sepsis • page 13

Problems Linger for ALI Survivors

BY MICHELE G. BULLIVAN
Elsevier Global Medical News

Survivors of acute lung injury are likely to experience depression and physical impairment for up to 2 years after leaving the intensive care unit. In a prospective study, 40% of patients had new-onset depression and 66% had new physical impairment after discharge. The findings seem inextricably linked on both psychological and physiological levels, Dr. Oscar J. Bienvenu and his colleagues wrote in the American Journal of Respiratory and Critical Care Medicine. “Depressive symptoms may decrease motivation for and reward from the physical activities necessary for recovery of maintenance of functioning. They can also amplify symptoms of general medical illnesses, and an increased physical symptom load could negatively affect functioning.” In addition, there may be less understood links between depression and physical functioning, wrote Dr. Bienvenu of

See ALI • page 18

Thinking about a change? Interested in relocating? Go where the jobs are …

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Sleep-Deprived Police Endanger Public Safety

BY MICHELE G. SULLIVAN

Early half of North American police officers suffering from a sleep disorder that could interfere with the safe execution of their duties. A survey of nearly 5,000 officers found that 40.4% of them screened positive for a sleep disorder, including obstructive sleep apnea, insomnia, restless legs syndrome, narcolepsy, and cataplexy. The survey also screened for shift-work disorder. Subjects provided basic health information, as well as information about alcohol intake and feelings of emotional burnout. They then completed monthly surveys for the next 2 years, with an accumulation of 15,735 surveys.

The mean age of the cohort was 38.5 years; 82.3% were male. More than half (58%) reported their health as very good or excellent. However, 79.3% of the respondents were overweight or obese, and 33.3% were obese.

Most were patrol officers (66.9%), followed by managers (15%), and criminal investigators (8.2%). Only 38% reported never having night-shift work; the rest worked overnight from one month per month to nearly every shift.

Of the entire cohort, 2,003 (40.4%) screened positive for at least one sleep disorder. Obstructive sleep apnea was the most commonly identified problem, affecting 1,666 (33.6%) of the participants. The next most commonly identified problem was moderate to severe insomnia, found in 281 (6.5%).

Other findings were shift-work disorder (5.4%), restless legs syndrome (1.4%), and narcolepsy with cataplexy (0.3%).

The group with shift-work disorder represented 14% of those who worked overnight hours, the investigators noted. However, they said, if they applied the International Classification of Sleep Disorders–2 criteria for shift-work disorder (excessive wake-time sleepiness or insomnia), 1,004 (53.9%) of the police officers who worked night shifts screened positive.

The investigators found some significant associations between sleep disorders and health/safety outcomes. Those with a positive screen were almost three times as likely to report depression (odds ratio, 2.75) and job burnout (OR, 2.87), and almost five times as likely to report having fallen asleep while driving after work (OR, 4.64). Of the entire cohort, 2,276 (46%) reported having fallen asleep while driving (56.9% at least once a month, and 13.5% once or twice a week).

At the 2-year follow-up, data were collected on 6,587 person-months for those with positive screens and 9,148 person-months for those with negative screens. Again, the authors found significant correlations between a sleep disorder and a behavioral or safety issue. Compared with those having a negative screen, those with a positive screen were 43% more likely to make an administrative error, 51% more likely to fall asleep while driving, and 63% more likely to make a fatigue-related safety error.

Sleep disorders also significantly correlated with public interaction. Those with positive screens were 23% more likely to experience uncontrolled anger at a citizen or suspect, and 33% more likely to incure a citizen complaint.

Over the follow-up period, those in the cohort experienced 287 motor vehicle accidents, which were 49% more common among those who had reported falling asleep while driving and 68% more common among those who reported falling asleep while stopped in traffic.

Most officers in the study were aware of their personal and performance problems, but they had no idea that a sleep disorder was a key factor.

“‘This study illustrates that the public at large may also be at risk when police officers are impaired in performing their duties because of sleep deprivation or an untreated sleep disorder,’” the authors said. Dr. Rajaratnam reported numerous financial relationships with pharmaceutical and medical device companies. The study was sponsored by the National Institute of Justice and the Centers for Disease Control and Prevention.
Pneumonia Vaccine Approved for Age 50 and Older

A pediatric pneumococcal vaccine has been approved for use in adults aged 50 years and older for preventing pneumonia and invasive disease caused by Streptococcus pneumoniae, the Food and Drug Administration announced.

The approval of Prevnar 13, a pneumococcal 13-valent conjugate vaccine, ‘provides an additional vaccine for preventing pneumococcal pneumonia and invasive disease in this age group,’ Dr. Karen Midthun, director of the FDA’s Center for Biologics Evaluation and Research, said in the statement announcing the approval. Pneumococcal disease is ‘a substantial cause of illness and death,’ and about 300,000 adults aged 50 years and older are hospitalized for pneumococcal pneumonia annually in the United States, she added.

Prevnar 13, manufactured by Wyeth Pharmaceuticals, a subsidiary of Pfizer, was approved in 2010 for children aged 6 months to 18 years for the prevention of invasive disease caused by 13 serotypes of S. pneumoniae, and for the prevention of otitis media caused by seven S. pneumoniae serotypes.

The approval of adults is an accelerated approval, which is used to approve products that have meaningful clinical benefit over existing treatments for serious and life-threatening illnesses, based on studies using surrogate effectiveness end points considered reasonably likely to predict clinical benefit. A product can be approved under the accelerated approval regulation if a follow-up clinical study confirming the anticipated clinical benefits is conducted.

The accelerated approval was based on randomized studies comparing immune responses to Prevnar 13 or Pneumovax 23 (a 23-valent pneumococcal vaccine approved in 1983 for children and for adults aged 50 and older) in more than 2,000 patients aged 50 and older in the United States and Europe. ‘The studies showed that the immune response to the 13 serotypes, Prevnar 13 induced antibody levels that were either comparable to or higher than the levels induced by Pneumovax 23,’ according to the FDA statement.

To meet postmarketing requirements, the manufacturer is conducting a study of more than 84,000 people aged 65 years and older who have not received Pneumovax 23. The goal is to evaluate whether Prevnar 13 is effective in preventing the first episode of community-acquired pneumonia caused by the 13 serotypes in the vaccine, according to the statement issued by Pfizer announcing the approval. The company is also conducting a study to evaluate the concomitant use of Prevnar 13 and the annual influenza vaccine in adults aged 59 years and older who have previously received the conventional pneumococcal polysaccharide vaccine.

Low-Dose Zolpidem Approved for Night Awakening

A low-dose sublingual formulation of zolpidem tartrate is the first agent to be approved to treat insomnia characterized by middle-of-the-night waking followed by difficulty returning to sleep, the FDA announced.

Zolpidem tartrate was first approved in the United States in 1992 as the highest dose formulation known as Ambien.

“For people whose insomnia causes them to wake in the middle of the night with difficulty returning to sleep, this new medication offers a safer choice than taking a higher dose of zolpidem upon waking,” said Dr. Robert Temple, deputy center director for clinical science in the FDA’s Center for Drug Evaluation and Research, in a statement. “With this lower dose, there is less risk of a person having too much drug in the body upon waking, which can cause dangerous drowsiness and impair driving.”

Intermezzo (Transcept Pharmaceuticals) should only be used when a person has at least 4 hours of bedtime remaining. It should not be taken if alcohol has been consumed or with any other sleep aid. The maximum dose of Intermezzo is 1.75 mg for women and 3.5 mg for men, taken once per night. The recommended dose for women is lower because women clear the substance from the body at a slower rate than men.

Intermezzo was studied in two clinical trials involving more than 370 patients. In the studies, patients taking the drug fell back to sleep faster after awakening, compared with those taking a placebo. The most commonly reported adverse reactions in the clinical trials were headache, nausea, and fatigue.

Potential side effects include getting out of bed while not fully awake and undertaking activities that are not remembered. Reported and not remembered activities have included driving a car, engaging in sexual activity, talking on the phone, and sleepwalking. Risks of such activities increase with use of alcohol or sedating drugs.

Intermezzo is a federally controlled substance.

Mortality Increased With Dronedarone and Permanent AF

Dronedarone increases the risk of death and serious cardiovascular events in people with permanent atrial fibrillation, and its use should be limited to the approved indication: the treatment of nonpermanent AF, the FDA has concluded.

In a statement, the FDA announced that its safety review of dronedarone, an antiarrhythmic drug approved in July 2009, has been completed. ‘The FDA believes that Multaq provides a benefit for patients with nonpermanent AF and recommends that health care professionals who prescribe Multaq follow the recommendations in the revised Multaq drug label,’ the FDA statement said.

Dronedarone, marketed as Multaq by Sanofi-Aventis, is indicated to “reduce hospitalizations for AF in patients in sinus rhythm with a history of nonpermanent AF.”

The FDA’s conclusions are based on a review of a large outcomes study that was meant to evaluate the effectiveness of dronedarone in more than 3,000 patients with permanent AF, but was terminated early when it became clear that cardiovascular events in this treatment group were higher among those treated with the drug than in those on placebo. In that study, PALLAS (Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy), the risk of total deaths was increased twofold among those treated with dronedarone compared with those on placebo. Also increased were the risks of death from arrhythmia or sudden death (hazard ratio, 3.26), stroke (HR, 2.32), and hospitalization for heart failure (HR, 1.81) over placebo.

The FDA’s reanalysis of the data from ATHENA, the clinical trial that supported the approval of dronedarone in patients with nonpermanent AF, found no increased risk of cardiovascular death, stroke, or heart failure among those on dronedarone compared with those on placebo, and treatment was associated with a reduced risk of hospitalizations.

The prescribing information for dronedarone has been revised to reflect the results of the safety review, and now advises against prescribing dronedarone to patients with AF who will not or cannot be converted into normal sinus rhythm, because “it doubles the rate of cardiovascular death, stroke, and heart failure in such patients.”

The label also recommends an electrocardiogram to monitor heart rhythm in patients on the drug at least once every 3 months, and if a patient is in AF, treatment should be stopped or, if clinically indicated, the patient should be cardioverted. Patients on dronedarone should also be on “appropriate antithrombotic therapy,” the label now states.

From July 2009 through October 2011, about 1.3 million dronedarone prescriptions were dispensed to about 278,000 patients received prescriptions for the drug from U.S. outpatient retail pharmacies, according to the FDA.

–Elizabeth Mechatie

Atrial Fibrillation Ablation Device Effective; Safety Uncertain

An FDA advisory panel did not support the approval of a catheter-based radiofrequency ablation device for treating persistent atrial fibrillation, citing concerns over safety issues.

At the meeting, the FDA’s Circulatory System Devices Panel voted 8 to 2 that the data on the Medtronic cardiac ablation system did not demonstrate that the benefits outweighed the risks of the device for the proposed indication: the treatment of symptomatic, drug refractory, persistent atrial fibrillation on long-standing persistent atrial fibrillation of up to 4 years in duration. Panelists described it as a pioneering and innovative device that was effective in a difficult-to-treat population and unanimously voted that there was “reasonable assurance” that it was effective for the proposed indication.

But they voted 9 to 1 that there was not reasonable assurance that it was safe, primarily because of the increased rate of strokes around the time of the procedure (3% of those treated with the device, compared with none among those treated medically) and the 4% rate of pulmonary vein stenosis and symptomatic narrowing of the pulmonary vein seen on CT or MRI 6 months after treatment with the device. Panelists were also concerned about reports in the literature of asymptomatic cerebrovascular emboli in patients treated with the device, which has been available in Europe since 2006, where it is approved for the treatment of paroxysmal atrial fibrillation.

In a prospective multicenter study of 210 patients with a history of symptomatic, refractory atrial fibrillation, patients were randomized to treatment with the device or medical treatment with new antiarrhythmic medications or titration of existing medication, in a 2:1 ratio. The primary end point of the study – acute procedural success and at least a 90% reduction in clinically significant AF/atrial flutter on 48-hour Holter at 6 months – was met by 56% of those treated with the device, compared with 26% of those who were medically managed, a statistically significant difference.

–Elizabeth Mechatie

Data Watch

Singular Among Potential Patent Expirations for 2012

Plavix (clopidogrel) $3.8

Singulair (montelukast) $3.5

Seroquel (quetiapine) $2.0

Actos (pioglitazone) $1.4

Lexapro (escitalopram) $1.4

Diovan (valsartan) $1.1

Diovan HCT (valsartan/HCTZ) $1.1

TriCor (fenofibrate) $0.5

2010 U.S. retail sales (billions)

Notes: Based on sales data from IMS Health. Availability dates for first-time generics are subject to significant change. Source: Medco.
Heparin Bridging Linked With Increased Bleeding Risk

BY DOUG BRUNK
Elsevier Global Medical News

SAN DIEGO – Patients who receive heparin bridging during an interruption of oral anticoagulation appear to be at a 5.4-fold increased risk of overall bleeding and a 3.6-fold increased risk of major bleeding, without a reduction in risk of thromboembolic events.

Those are key findings from a systematic review and meta-analysis of recently published medical literature presented by Dr. Jovana Yudin at the annual meeting of the American Society of Hematology.

Antithrombotic and thrombolytic therapy guidelines published by the American College of Chest Physicians in 2008 recommended bridging according to an individualized approach (Chest 2008;133[suppl. 6]:2985-3305). "They suggested bridging according to patients' bleeding and thromboembolic risk," said Dr. Yudin, a fellow in the hematology residency program at McMaster University, Hamilton, Ont. "Within the last decade, several new studies have been published using periprocedural bridging. In these studies, low-molecular-weight heparin has been used with increased frequency. However, optimal strategies for bridging remain unclear. Our objective was to do a systematic review and meta-analysis of bridging trials published in the last decade to look at thromboembolic risk as well as bleeding risk."

Dr. Yudin and her associates searched the MEDLINE, EMBASE, and Cochrane Collaboration databases for systematic reviews and meta-analyses of studies published between Jan. 1, 2001, and July 31, 2010, that examined bleeding and thromboembolic events in patients receiving bridging therapy during temporary oral anticoagulation interruption for elective surgical or invasive procedures. Studies were excluded if the reporting of thromboembolic or bleeding outcomes was unclear, or if they focused exclusively on patients with renal failure. All studies were reviewed by two independent investigators.

The researchers identified and screened 1,164 studies for review. Of these, 35 studies that included 7,169 bridged patients were selected for the final review. Most of the studies (33) were observational, and only two were randomized. The median follow-up was 30 days. The most common indication for anticoagulation was atrial fibrillation (44%), followed by mechanical valve (24%), prior venous thromboembolism (22%), and other (10%).

The most common preoperative strategy was to discontinue oral anticoagulation more than 3 days in advance. Low-molecular-weight heparin was most commonly used, both preoperatively and postoperatively.

Dr. Yudin reported that thromboembolic events, which were primarily arterial in nature, occurred in 7% of the 7,169 patients (mean rate, 0.96%). The mean rate of overall bleeding was 13.01%, whereas the mean rate of major bleeding was 4.32%.

Eight of the studies included in the final analysis had control groups from which the researchers were able to pull data to determine an odds ratio for thromboembolism with bridging vs. no bridging. These studies included 1,691 bridged patients and 3,493 nonbridged patients. The odds ratio for thromboembolism was 1.80, with a 95% CI of 1.02-3.15, "suggesting no risk reduction for thromboembolic events with heparin or low-molecular-weight bridging."

Less Bleeding, Shorter Stay

Rivaroxaban • from page 1

Dr. Yudin said that she had no relevant financial conflicts to disclose.

To determine the risk of overall bleeding, the researchers pulled data from 13 studies that included control groups. These studies included 1,985 bridged patients and 5,160 nonbridged patients. The odds ratio for overall bleeding with bridging was 5.40 (95% CI, 3.00-9.74). "This suggested an increased risk of overall bleeding with bridging anticoagulation, but there was significant heterogeneity noted across these studies."

For major bleeding, five studies with control groups were assessed. These included 1,397 bridged patients and 2,104 nonbridged patients. The odds ratio for major bleeding was 3.60 (95% CI, 1.52-8.30), "again suggesting an increased risk in major bleeding with bridging," she said. "There was significant heterogeneity noted across studies."

Dr. Yudin acknowledged that the review had certain limitations. Most of the studies included in the analysis were observational, and only about a third had control groups. "Our control groups consisted largely of low-thromboembolism-risk patients, or patients who were not chronically on vitamin K antagonists, suggesting that they had a different risk profile for thromboembolism than many of the bridged patients," she said.

The findings "underline the need for studies of higher [methodological] quality in periprocedural bridging," she concluded. "It also tells us that there is a need for standardized definitions in terms of outcomes. We suspect that much of our heterogeneity had to do with varying definitions for outcomes such as major bleeding."

Disclosures: Dr. Yudin said that she had no relevant financial conflicts to disclose.

Dr. Yudin said, "There was also no difference between these two groups in the risk for arterial or venous thromboembolism."

"Vital Signs”

Major Finding: Patients who received heparin bridging during (interruption of oral anticoagulation) had a significantly increased risk of overall bleeding (odds ratio 5.4) and major bleeding (GR 3.6), compared with nonbridged patients.

Data Source: A meta-analysis of 35 studies that examined bleeding and thromboembolic events in patients receiving bridging therapy during temporary interruption of oral anticoagulants for elective procedures.

Disclosures: Dr. Yudin said that she had no relevant financial conflicts to disclose.

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Disclosures: Dr. Yudin said that she had no relevant financial conflicts to disclose.
COPD EXACERBATIONS are serious events...

Reducing Patient Risk Is Critical

INDICATIONS AND USAGE
DALIRESP is indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. DALIRESP is not a bronchodilator and is not indicated for the relief of acute bronchospasm.

Please see Important Safety Information and Brief Summary of full Prescribing Information on the following pages and at www.DALIRESP.com.

COPD=chronic obstructive pulmonary disease.
IMPORTANT SAFETY INFORMATION

Contraindications

DALIRESP is contraindicated in patients with moderate to severe liver impairment (Child-Pugh B or C).

Warnings and Precautions

• DALIRESP is not a bronchodilator and should not be used for the relief of acute bronchospasm.

• Prescribers should advise patients, their caregivers, and families to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if such changes occur, to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment if such events occur. Before using DALIRESP in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with DALIRESP.

– Treatment with DALIRESP is associated with an increase in psychiatric adverse reactions. In controlled clinical trials 5.9% of patients treated with DALIRESP reported psychiatric adverse reactions vs 3.3% treated with placebo. The most common psychiatric adverse reactions were insomnia (2.4% vs 1.0%), anxiety (1.4% vs 0.9%), and depression (1.2% vs 0.9%).

– Three patients treated with DALIRESP experienced suicide-related adverse reactions (one completed suicide and two suicide attempts) compared to one patient (suicidal ideation) treated with placebo.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the following pages and at www.DALIRESP.com.
For patients with severe COPD associated with chronic bronchitis and a history of exacerbations

TREAT NOW WITH DALIRESP®

The first and only selective PDE4 inhibitor to reduce the risk of COPD exacerbations

- Reduces moderate or severe exacerbations by 17% vs placebo
- Effective alone or in combination with a bronchodilator
- Effective in older and younger patients (>65 and 40-65 years)
- Statistically significant increase in lung function (pre-bronchodilator FEV₁) of 48 mL vs placebo
  - DALIRESP is not a bronchodilator; this increase was not clinically significant
- The first class of drugs approved for COPD in 25 years

- Patients should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated and treatment discontinuation considered.
  - In addition to weight loss being reported as a common adverse reaction (7.5% of patients treated with DALIRESP vs 2.1% placebo), weight was prospectively assessed in two 1-year clinical trials. In these studies that compared DALIRESP to placebo, 20% vs 7% experienced moderate weight loss (5-10% of body weight) and 7% vs 2% experienced severe weight loss (>10% body weight).
  - During the follow-up period after discontinuing DALIRESP, the majority of patients regained some of the weight they had lost.
- Use with strong cytochrome P450 enzyme inducers (eg, rifampicin, phenobarbital, carbamazepine, phenytoin) is not recommended, as they decrease the exposure and may reduce the therapeutic effectiveness of DALIRESP.

Daliresp® (roflumilast) tablets 500 mcg
For patients with severe COPD associated with chronic bronchitis and a history of exacerbations

**DALIRESP** significantly reduces exacerbations

**REduction in the rate of moderate or severe exacerbations**

- **Placebo** (n=1554): Mean Number of Exacerbations per Patient per Year = 1.37
- **DALIRESP** (n=1537): Mean Number of Exacerbations per Patient per Year = 1.14

\[ P = 0.0003 \text{ vs placebo} \]

**Study design:** A pre-specified pooled analysis from 2 identical, 52-week, double-blind, placebo-controlled trials in patients with severe COPD associated with chronic bronchitis and a history of exacerbations (N=3091). Median patient age was 64 years; 76% male, 84% Caucasian. LABAs or short-acting anticholinergics were allowed as concomitant treatment. The reduction in the rate of moderate (requiring treatment with systemic glucocorticosteroids) or severe (resulting in hospitalization and/or leading to death) exacerbations and change in lung function (pre-bronchodilator FEV₁) were co-primary endpoints. Each study met both co-primary endpoints.

- **Moderate exacerbations** were defined as those requiring treatment with systemic corticosteroids
- **Severe exacerbations** were defined as resulting in hospitalization and/or death

**INDICATIONS AND USAGE**
DALIRESP is indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. DALIRESP is not a bronchodilator and is not indicated for the relief of acute bronchospasm.

**IMPORTANT SAFETY INFORMATION**

**Warnings and Precautions**

- Prescribers should advise patients, their caregivers, and families to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if such changes occur, to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment if such events occur. Before using DALIRESP in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with DALIRESP.

**References:**
For patients with severe COPD associated with chronic bronchitis and a history of exacerbations

Effective with LABAs or short-acting anticholinergics

**In the same studies:**

DALIRESP significantly reduced the rate of exacerbations vs placebo in patients using a bronchodilator\(^1,3\)

**Study design:** A pre-specified pooled analysis from 2 identical, 52-week, double-blind, placebo-controlled trials in patients with severe COPD associated with chronic bronchitis and a history of exacerbations (N=3091). Median patient age was 64 years; 76% male, 84% Caucasian. LABAs and short-acting anticholinergics were allowed and were used by 44% and 35% of patients treated with DALIRESP and 45% and 37% of patients treated with placebo, respectively. The reduction in the rate of moderate (requiring treatment with systemic glucocorticosteroids) or severe (resulting in hospitalization and/or leading to death) exacerbations and change in lung function (pre-bronchodilator FEV\(_1\)) were co-primary endpoints. Each study met both co-primary endpoints.

- The effect with concomitant LABAs or short-acting anticholinergics was similar to that seen in the overall population\(^1,3\)

**IMPORTANT SAFETY INFORMATION**

**Warnings and Precautions**
- Patients should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated and treatment discontinuation considered.

**Adverse Reactions**
In clinical trials the most common adverse reactions (\(\geq 2\%\) and greater than placebo) were diarrhea (9.5% vs 2.7%), weight loss (7.5% vs 2.1%), nausea (4.7% vs 1.4%), headache (4.4% vs 2.1%), back pain (3.2% vs 2.2%), influenza (2.8% vs 2.7%), insomnia (2.4% vs 1.0%), dizziness (2.1% vs 1.1%), and decreased appetite (2.1% vs 0.4%).

Please see additional Important Safety Information on the previous pages and Brief Summary of full Prescribing Information on the following page and at [www.DALIRESP.com](http://www.DALIRESP.com).
DALIRESP® (roflumilast) tablets
Rx Only
Brief Summary of Full Prescribing Information

Initial U.S. Approval: 2011

INDICATIONS AND USAGE
DALIRESP® is indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.

Limitations: DALIRESP is not a bronchodilator and is not indicated for the relief of acute bronchospasm.

CONTRAINdications
The use of DALIRESP is contraindicated in the following conditions:
• Moderate to severe liver impairment (Child-Pugh B or C) [see Clinical Pharmacology (12.3) and Use in Special Populations (8.6)].

WARNINGS AND PRECAUTIONS
Treatment of Acute Bronchospasm
DALIRESP is not a bronchodilator and should not be used for the relief of acute bronchospasm.

Psychiatric Events Including Suicidality
Treatment with DALIRESP is associated with an increase in psychiatric adverse reactions. In 8 controlled clinical trials 5.9% (263) of patients treated with DALIRESP 500 mcg daily reported psychiatric adverse reactions compared to 3.3% (137) treated with placebo. The most commonly reported psychiatric adverse reactions were insomnia, anxiety, and depression which were reported at higher rates in those treated with DALIRESP 500 mcg daily (2.4%, 1.4%, and 1.2% for DALIRESP versus 1.0%, 0.9%, and 0.9% for placebo, respectively) [see Adverse Reactions (6.1)]. Instances of suicidal ideation and behavior, including completed suicide, have been observed in clinical trials. Three patients experienced suicide-related adverse reactions (one completed suicide and two suicide attempts) while receiving DALIRESP compared to one patient (suicidation) who received placebo.

Before using DALIRESP in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with DALIRESP in such patients. Patients, their caregivers, and families should be advised to be alert for any emerging or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with DALIRESP if such events occur.

Weight Decrease
Weight loss was a common adverse reaction in DALIRESP clinical trials and was reported in 7.5% (221) of patients treated with DALIRESP 500 mcg once daily compared to 2.1% (89) treated with placebo [see Adverse Reactions (6.1)]. It is recommended that the dose of other concomitant medications be titrated to maintain the same weight as observed at the beginning of treatment. In cases of weight loss greater than 10%, the dose of DALIRESP should be reduced as soon as possible.

Adverse Reactions
The following adverse reactions are described in greater detail in other sections:
• Psychiatric Events Including Suicidality [see Warnings and Precautions (5.3)]
• Weight Decrease [see Warnings and Precautions (5.3)]

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

The safety data described below reflect exposure of 4438 patients to DALIRESP 500 mcg once daily in four 1-year placebo-controlled trials, two 6-month placebo-controlled trials, and two 6-month drug-add-on trials [see Clinical Studies (14.1)]. In these trials, 3136 and 1322 COPD patients were exposed to DALIRESP 500 mcg once daily for 6 months and 1-year, respectively.

The population had a median age of 64 years (range 40-91), 73% were male, 92.9% were Caucasian, and had COPD with a forced expiratory volume in one second (FEV1) of 8.8 to 88.1% predicted. In these trials, 68.5% of the patients treated with DALIRESP reported an adverse reaction compared to 65.3% treated with placebo.

The proportion of patients who discontinued treatment due to adverse reaction was 14.8% for DALIRESP-treated patients and 9.6% for placebo-treated patients. The most common adverse reactions that led to discontinuation of DALIRESP were diarrhea (2.4%) and nausea (1.8%).

Serious adverse reactions, whether considered drug-related or not by the investigator, which occurred more frequently in DALIRESP-treated patients include, diarrhea, abdominal pain, lung cancer, prostate cancer, acute pancreatitis, and acute renal failure. Table 1 summarizes the adverse reactions reported by ≥ 2% of patients in the DALIRESP group in 8 controlled COPD clinical trials.

Table 1: Adverse Reactions Reported by ≥ 2% of Patients Treated with DALIRESP 500 mcg daily compared to Placebo

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Adverse Reactions (Preferred Term)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DALIRESP</td>
<td>PHARMACIST</td>
</tr>
<tr>
<td>Placebo</td>
<td>(Both)</td>
</tr>
<tr>
<td>N (N=1230)</td>
<td>N (N=1230)</td>
</tr>
<tr>
<td>GI disturbances</td>
<td>102 (8.3)</td>
</tr>
<tr>
<td>constipation</td>
<td>28 (2.3)</td>
</tr>
<tr>
<td>diarrhea</td>
<td>20 (1.6)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>190 (15.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>202 (16.5)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>124 (10.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>105 (8.5)</td>
</tr>
<tr>
<td>Nervousness</td>
<td>97 (7.9)</td>
</tr>
</tbody>
</table>
| Adverse reactions that occurred in the DALIRESP group at a frequency of 1 to 2% where rates exceeded that in the placebo group include:
- Gastrointestinal disorders - abdominal pain, dyspepsia, gas, vomiting
- Infections and infestations - thrush, sinuses, urinary tract infection.

Psychiatric disorders - anxiety, depression

DRUG INTERACTIONS
A major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP2A4 and CYP1A2 [see Clinical Pharmacology (12.3)].

Drugs That Induce Cytchrome P450 (CYP) Enzymes
Strong cytochrome P450 enzyme inducers decrease systemic exposure to roflumilast and may reduce the therapeutic effectiveness of DALIRESP, therefore the use of strong cytochrome P450 inducers (e.g., rifampicin, phenobarbital, carbamazepine, and phenytoin) with DALIRESP is not recommended [see Drug Interactions (5.4) and Clinical Pharmacology (12.3)].

Drugs That Inhibit Cytchrome P450 (CYP) Enzymes
The co-administration of DALIRESP (500 mcg) with CYP3A4 inhibitors or dual inhibitors that inhibit both CYP3A4 and CYP1A2 simultaneously (e.g., erythromycin, ketoconazole, fluvoxamine, escin, cimetidine) may increase roflumilast systemic exposure and may result in increased adverse reactions. The risk of such concurrent use should be weighed carefully against benefit [see Clinical Pharmacology (12.3)].

Oral Contraceptives Containing Gestodene and Ethinyl Estradiol
The administration of DALIRESP (500 mcg) with oral contraceptives containing gestodene and ethinyl estradiol may increase roflumilast systemic exposure and may result in increased side effects. The risk of such concurrent use should be weighed carefully against benefit [see Clinical Pharmacology (12.3)].

USE IN SPECIFIC POPULATIONS

Pregnancy
Teratogenic effects: Pregnancy Category C. There are no adequate and well-controlled studies of DALIRESP in pregnant women. DALIRESP was not teratogenic in mice, rats, or rabbits. DALIRESP should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

DALIRESP induced stillbirth and decreased pup viability in mice at doses corresponding to approximately 16 and 49 times, respectively, the maximum recommended human dose (MRHD) (on a mg/m² basis at maternal doses ≥ 2 mg/kg/day and 6 mg/kg/day, respectively). DALIRESP induced post-implantation loss in rats at doses greater than or equal to approximately 10 times the MRHD (on a mg/m² basis at maternal doses ≥ 0.6 mg/kg/day). No treatment-related effects on embryo-fetal development were observed in mice, rats, and rabbits at approximately 12, 2, and 26 times the MRHD, respectively (on a mg/m² basis at maternal doses of 1.0, 0.2, and 0.8 mg/kg/day, respectively).

Nonteratogenic effects: DALIRESP has been shown to adversely affect pup postnatal development when dams were treated with the drug during pregnancy and lactation periods in mice. These studies found that DALIRESP decreased pup rearing and increased pup mortality by 9% and 1%, respectively, at maternal doses of 12 and 0.1 mg/kg/day (on a mg/m² basis at a maternal dose of 6 mg/kg/day) during pregnancy and lactation. DALIRESP also decreased survival and forelimb grip reflex and delayed pinna detachment in mouse pups at approximately 97 times the MRHD (on a mg/m² basis at maternal doses ≥ 2 mg/kg/day).

Labor and Delivery
Labor and delivery should not be used during labor and delivery. There are no human studies that have investigated the effects of DALIRESP on preterm or labor at term; however, animal studies showed that DALIRESP disrupted the labor and delivery process in mice. DALIRESP induced delivery retardation in pregnant mice at doses greater than or equal to approximately 16 times the MRHD (on a mg/m² basis at a maternal dose of ≥ 2 mg/kg/day).

Nursing Mothers
DALIRESP and/or its metabolites are excreted into the milk of lactating rats. Excretion of roflumilast and/or its metabolites into human milk is probable. There are no human studies that have investigated effects of DALIRESP on breast-fed infants. DALIRESP should not be used by women who are nursing.

Pediatric Use
The safety and effectiveness of DALIRESP in pediatric patients have not been established.

Geriatric Use
COPD does not normally occur in children. The safety and effectiveness of DALIRESP in pediatric patients have not been established.

OVERDOSAGE

Human Experience
No case of overdose has been reported in clinical studies with DALIRESP. During the Phase 1 studies of DALIRESP, the following symptoms were observed at an increased rate after a single oral dose of 2500 mg and a single dose of 5000 mg: headache, gastrointestinal disorders, dizziness, palpitations, lightheadedness, clamminess, and arterial hypotension.

Management of Overdose
In case of overdose, patients should seek immediate medical help. Appropriate supportive medical care should be provided. Since roflumilast is highly protein bound, it is unlikely that it would be dialyzable by peritoneal dialysis. Manufactured by:
Nycomed GmbH, Production Site Oranienburg, Germany 16515 Oranienburg, Germany Manufactured for:
Forest Laboratories, Inc., Subsidiary of Forest Laboratories, Inc. St. Louis, MO 63045, USA

Daliresp® is a registered trademark of Nycomed GmbH. © 2010, 2011 Forest Laboratories, Inc. 084-12000414-B-T-RMCL17127-SEP11 Please also see full Prescribing Information at www.daliresp.com.
MITH Score Uses Admission Criteria to Predict VTE

**BY DOUG BRUNK**
Elsevier Global Medical News

SAN DIEGO – The three most significant risk factors for venous thromboembolism among medical inpatients were a history of congestive heart failure or of rheumatologic or inflammatory disease and having a fracture in the past 3 months.

Those are findings from a study of a risk assessment model known as the Medical Inpatients and Thrombosis (MITH) score, which was developed to help clinicians assess venous thromboembolism (VTE) risk at admission for medical inpatients. The score relies on assessing risk factors at admission.

"The few current risk assessment models for hospital-acquired VTE have many limitations," Dr. Neil A. Zakai said at the annual meeting of the American Society of Hematology. "Some of these are empirically derived. Others are derived from selected medical populations such as restricting hospital stays more than 3 days and restricting patient age, and others have difficult-to-ascertain VTE risk factors such as anticipated bed confinement or hypercoagulable states that may or may not be documented in the medical record."

Dr. Zakai, of the department of medicine and pathology at the University of Vermont, Burlington, and associates studied an unselected medical population and included all VTE events. They conducted a frequency-matched case-control study at a 500-bed teaching hospital in Vermont. They studied 299 cases of hospital-acquired VTE that occurred between Jan. 1, 2002, and May 31, 2009, using ICD-9-CM discharge codes, and validated the cases by medical record review. A total of 601 controls were frequency matched by admission service and year.

Risk factors for VTE were collected at admission as part of routine medical care. "Models were built using clinical judgment; we didn't use automatic selection algorithms," Dr. Zakai explained. "Points were assigned for each risk factor by dividing the beta values by the lowest beta value in the model and rounding to the nearest integer. Models were validated using multiple permutation methods."

Dr. Zakai reported that the VTE event rate during the study period was 4.6 per 1,000 admissions. About half of the events (154) were DVT plus or minus pulmonary embolism.

"What's remarkable is the large number of upper-extremity DVTs, representing approximately half of all DVTs in this population," he said.

Most of the VTE events occurred on the general medicine service (an incidence of 8 per 1,000 admissions), followed by the oncology service (7.6 per 1,000 admissions) and the cardiology service (1.1 per 1,000 admissions).

Nine admission factors were significantly associated with a risk of VTE: history of congestive heart failure (odds ratio 8.6, and a score of 5 on the MITH scale), history of rheumatic or inflammatory disease (OR 7.7, and a score of 4 on the MITH scale), history of pulmonary or inflammatory disease (OR 7.7, and a score of 4 on the MITH scale), fracture in the past three months (OR 3.8, and a score of 3 on the MITH scale), DVT prophylaxis at death (OR 1.5, and a score of 2 on the MITH scale), tachycardia (OR 2.5, and a score of 2 on the MITH scale), respiratory dysfunction (OR 1.9, and a score of 1 on the MITH scale), white blood cell count of 11 or greater (OR 1.9, and a score of 1 on the MITH scale), and a platelet count of 350 or greater (OR 1.9, and a score of 1 on the MITH scale). Each of these risk factors was assigned a point value, which could range from 1 to 5.

A high risk of VTE was attributed to anyone with a score of 2 points or greater on the MITH scale. Using this definition, 70% of cases and 39% of controls were classified as high risk.

The probability of venous thromboembolism in the absence of prophylaxis was 1.5 per 1,000 admissions in those with a MITH score of less than 2 and 8.9 per 1,000 admissions for those with a MITH score of 2 or greater.

Using validation and sensitivity analysis, the researchers determined that the c-statistic for the model was 0.73 (95% confidence interval, 0.70-0.76) and 0.71 when the lab studies on admission were excluded (95% CI, 0.68-0.74).

Limitations of the study include its single-center design and the fact that the findings are validated by statistical means only. "Patients with rare risk factors may be misclassified as low risk, and the level of VTE risk warranting prophylaxis is not established," Dr. Zakai said.

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**COMMENTARY**

Dr. Carl Kaplan, FCCP, comments: This is a new, thoughtful prediction and risk assessment tool for medical patients at the time of admission relating to venous thrombosis, the Medical Inpatient and Thrombosis (MITH) score. The importance of prevention of venous thromboembolism for every hospitalized patient is highlighted in our guidelines and centers around risk assessment. We need a multicenter prospective validation study with the assessment of event reduction with adequate prophylaxis and low adverse events.

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**Statin May Cut Atrial Fibrillation Risk**

**BY BRUCE JANCIN**
Elsevier Global Medical News

ORLANDO – The higher a patient’s baseline high-sensitivity C-reactive protein level in the landmark JUPITER study, the greater the incidence of new-onset atrial fibrillation during follow-up, and randomization to rosuvastatin significantly reduced this risk.

**Major Finding:** Apparently healthy subjects with high C-reactive protein and an LDL below 130 mg/dL who were placed on rosuvastatin at 20 mg/day had a 27% lower incidence of new-onset atrial fibrillation than placebo-treated controls during a mean of 1.9 years of follow-up.

**Data Source:** Double-blind, randomized JUPITER study.

**Disclosures:** JUPITER was sponsored by AstraZeneca. Dr. Peña reported having no relevant conflicts of interest.

Among the 17,120 apparently healthy participants in JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) with no baseline history of atrial fibrillation or other arrhythmia, those in the highest baseline tertile for C-reactive protein (CRP) – that is, more than 5.8 mg/L – had an adjusted 1.96-fold greater incidence of new-onset atrial fibrillation during follow-up, compared with those in the lowest tertile for the inflammatory biomarker, with a CRP of less than 3.2 mg/L. Dr. Jessica M. Peña reported at the annual scientific sessions of the American Heart Association.

Those in the middle tertile had a 1.7-fold increased risk of developing atrial fibrillation after adjustment for age, gender, race, exercise, alcohol intake, current smoking, metabolic syndrome, hypertension, body mass index, and glycosylated hemoglobin.

The incidence of new-onset atrial fibrillation was 0.81 cases per 100 person-years in subjects in the top tertile for baseline CRP 0.75 per 100 person-years for those in the middle tertile, and 0.43 per 100 person-years among patients in the lowest tertile, according to Dr. Peña of Brigham and Women’s Hospital, Boston.

Rosuvastatin (Crestor) proved to have a significant impact upon this risk. The crude incidence was 1.6% with placebo, compared to 1.2% with the statin, which worked out to an adjusted 27% reduction in relative risk in the rosuvastatin group.

The presumed mechanism of benefit lies in the mounting evidence suggesting that inflammation plays a role in both the initiation and maintenance of atrial fibrillation. Statins have anti-inflammatory properties that could be helpful in preventing the arrhythmia, she observed.

In this post hoc analysis, atrial fibrillation was not a prespecified study end point, Dr. Peña stressed. She and her coinvestigators undertook this exploratory analysis because other studies have yielded mixed results regarding statins and atrial fibrillation. The JUPITER analysis provided an opportunity to focus on a population with an underlying proinflammatory state as manifest by the requirement that participants had to have a baseline CRP of at least 2 mg/L.

A recent meta-analysis of atrial fibrillation found that the available evidence does not support the notion that statins reduce atrial fibrillation risk (BMJ 2011;342:d1250). Dr. Peña surmised that the different study conclusions were probably due to different populations and methods of detecting atrial fibrillation. "Until we have better data we can't definitively answer the question of whether statins protect against atrial fibrillation," Dr. Peña said.

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Dr. Jun Chiang, FCCP comments: It is comforting to know that what we commonly do to slow the progression of coronary disease can also cut the risk for atrial fibrillation. However, secondary analysis only proves association and the hypothesis generated has to be tested in a randomized setting.
The new facility, located in Holly Springs, N.C., culminates a 7-year project by Novartis working on contract with the Health and Human Services department.
They assessed the organs of 40 patients who died while being treated for sepsis in surgical or medical intensive care units, and control samples from 29 patients who had critical illnesses that did not involve sepsis. The control tissue came from organ donors, trauma patients who required emergency splenectomy, and non-tumor-involved lung tissue from lung cancer patients who underwent lobectomies.

The causes of sepsis included ventilator-associated pneumonia, peritonitis, necrotizing fasciitis, retroperitoneal abscess, infected intravascular catheters, urinary tract infection, intraepelic abscess, and osteomyelitis.

Compared with cells from control spleens, splenocytes from sepsis patients showed profound impairment of cytokine production when stimulated in vitro. At 5 hours after collection, the secretion of cytokines from splenocytes of sepsis patients was less than 10% of that secreted by control splenocytes, the investigators said (JAMA 2011;306:2594-605).

Splenocytes from most sepsis patients showed some recovery of cytokine production at 22 hours, but they still secreted only one-third the number of cytokines produced by control splenocytes. This result was consistent for all the cytokines tested and for all subgroups of patients, regardless of the duration of sepsis, patient age, whether corticosteroids had been received, and patient nutritional status at the time of death.

The researchers identified many separate mechanisms by which immune responses were inhibited in spleen cells. They found a decrease in stimulatory molecules such as CD28 on T cells, a decrease in antigen-presenting cells such as macrophages and dendritic cells, increased expression of inhibitory ligands that suppress immune function, and an excess of inhibitory cells such as myeloid-derived suppressor cells and regulatory T cells.

Lung tissue similarly showed significant immunosuppression in sepsis patients, compared with control patients. In particular, lung alveolar epithelial cells and endothelial cells showed an excess of inhibitory receptors and ligands.

The study findings suggest that it may be possible to identify sepsis patients who enter this phase of immunocompromise and treat them with immune-enhancing therapies such as interleukin, the researchers said.

The study was limited by its small sample size and the heterogeneous nature of both the sepsis and control patients, the authors said. They further emphasized that malnutrition should be recognized for its possible effects on host immunity and that for a number of reasons, their study “must be viewed cautiously.” The research “serves as a bridge between preclinical and early clinical findings,” they wrote.

This study was supported by the National Institutes of Health. One coauthor reported receiving grants from Pfizer, Bristol-Myers Squibb, and Aurigene.
Seizing a Seizure? Look for Pulmonary Embolism

BY MICHELE G. SULLIVAN
Elsevier Global Medical News

BALTIMORE–A seizure was initially the only presenting symptom in 15% of patients diagnosed with pulmonary embolism during a 5-year retrospective study of cases seen at an emergency department. Although it is an unusual presentation, pulmonary embolism–related seizure does occur, and when it does, it’s a life-threatening emergency, Dr. Kimotshi Kimura reported in a poster at the annual meeting of the American Epilepsy Society. With a seizure, clinical evaluation may be compromised by the postural confusional state. Hypoxia, tachypnea, and tachycardia, which are important signs of PE, may be attributed to the seizure. This results in delayed diagnosis,” said Dr. Kimura.

Kimura was propelled to the study when he was attending the 2011 annual meeting of the American Epilepsy Society in New York City. At the meeting, he listened to a presentation by Dr. Shinya Kurosawa, a neurologist who practices in Osaka, Japan. "It was a case report of a patient who presented as a status epilepticus, but had been diagnosed already in cardiopulmonary arrest. The patient died the next day in the intensive care unit. The patient was in his 70s, had been treated successfully with heparin. But, it was an unusual cause of death,” Kimura noted. The embolism persisted,” Dr. Kimura wrote.

At first, we suspected the cause of the seizures was a cerebral hemorrhage or a stroke. But then we suspected the pulmonary embolism related to cerebral hemorrhage or a stroke. It was all possible, given the history of the patient’s medical conditions and the fact that the patient was a smoker," Kurosawa wrote.

The patient had a chronic obstructive pulmonary disease (COPD) and a history of smoking. His age was 72 and he had been treated with heparin for 34 cases. He died because of a PE diagnosis, Kurosawa noted. His embolism was underdiagnosed," he said.

Two cases of pulmonary embolism reported at the American Epilepsy Society meeting at the time of the presentation were included in the final report. One involved a 78-year-old man who died of an embolism while in cardiopulmonary arrest. The second involved a 35-year-old woman who complained of chest discomfort while at home. The next morning, she experienced generalized tonic seizures with conjugated deviation; the seizures occurred intermittently for 4 hours. She was admitted to the hospital and received four 5-mg doses of diazepam. When the seizures stopped, the patient had partial resolution of hypoxia and an elevated D-dimer of more than 10 mg/mL (normal is less than 1.0 mg/mL). Mild right ventricular overload and PE were detected.

"In this case, she was treated successfully with anticoagulation therapy," Dr. Kimura wrote.

The third patient was a 78-year-old woman admitted because of a 5-minute generalized tonic seizure and drowsiness. After the seizure, she also remained hypoxic and had a D-dimer value of 2.3 mg/mL. At first, we suspected the cause of the seizure was a cerebral hemorrhage or a stroke. But then we suspected the pulmonary embolism related to cerebral hemorrhage or a stroke. It was all possible, given the history of the patient’s medical conditions and the fact that the patient was a smoker," Kurosawa wrote.

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No Lung Damage Seen in Typical Marijuana Smokers

BY MARY ANN MOON
Elsevier Global Medical News

Unlike cigarette smoking, 20 years of typical marijuana smoking doesn’t appear to impair lung function, according to a report in JAMA.

With up to 7 joint-years of lifetime exposure (e.g., one joint per day for 7 years or one joint per week for 49 years), we found no evidence that increasing exposure to marijuana adversely affects pulmonary function,” said Dr. Mark J. Fletcher of the department of epidemiology and biostatistics and the department of medicine, University of California, San Francisco, and his associates.

While heavier use may impair lung function, the number of such users was too small in this study cohort to allow reliable estimates, the investigators noted.

Previous studies of the pulmonary effects of long-term marijuana use have yielded inconsistent results. Some have demonstrated “consistent evidence of airway mucosal injury and inflammation, as well as increased respiratory symptoms such as cough, phlegm production, and wheeze, similar to that seen in tobacco smokers.” However, these appear to be short-term effects, and there has been no clear evidence of long-term damage to lung function.

Dr. Fletcher and his colleagues used data from a large longitudinal study of coronary risk that closely followed the cigarette and marijuana smoking habits of 5,016 young adults in four U.S. communities from 1985 through 2006. As part of that study, the subjects (aged 18-30 years at baseline) underwent pulmonary function testing at baseline, 2 years, 5 years, 10 years, and 20 years. Using that data, “we estimated both current intensity and lifetime cumulative exposure to tobacco and marijuana smoking and analyzed their associations with spirometric measures of pulmonary function over the 20 years of follow-up,” the researchers said.

As expected, both current and lifetime tobacco smoking were associated with lower forced expiratory volume in 1 second (FEV1) and lower forced vital capacity (FVC). But unexpectedly, both current and lifetime marijuana smoking were associated with higher FEV1 and higher FVC, the authors wrote (JAMA 2012;307:173-81).

Why marijuana smoking would increase lung capacity is unknown, but other studies have also found this effect. “Some investigators have proposed that the deep inspiratory maneuvers practiced by marijuana smokers could stretch the lungs, resulting in larger lung volumes. Another speculative possibility is strengthening of chest wall musculature or another ‘training’ effect that allows marijuana users to inspire more fully (closer to lung capacity) on spirometry testing,” Dr. Fletcher and his associates said. Only at very high levels of marijuana smoking was a detrimental effect on pulmonary function suggested.

This study was supported by the National Institute on Drug Abuse and the National Heart, Lung, and Blood Institute. Dr. Fletcher reported no conflicts of interest.

Only at very high levels of marijuana smoking was a detrimental effect on pulmonary function suggested.
Recommendations Made for Off-Label Cancer Treatments

BY ELIZABETH MECHCATTIE
Elsevier Global Medical News

Prospective clinical studies that evaluate off-label uses of approved oncology drugs for advanced cancers should include patients in community settings and, whenever possible, should use actual survival as the primary outcome instead of a surrogate for survival, according to recommendations published online in the Journal of Clinical Oncology.

These and other proposed recommendations are outlined in a document intended "to guide the design of future prospective trials for off-label use of oncology drugs," wrote C. Daniel Mullins, Ph.D., professor of pharmacoeconomics at the University of Maryland, School of Pharmacy, Baltimore, and his coauthors, in the paper (doi:10.1200/JCO.2011.35.5198). "The recommendations "address the needs of patients and their clinical providers, compendia, payers, and policy makers,"

The document is intended to "guide the design of future prospective trials for off-label use of oncology drugs."

DR. MULLINS

and have gone beyond first-line treatments. (The CMTP is a private, non-profit organization, which "serves as a neutral forum to promote discussion and development strategies that improve the quality of clinical research for health care decision making," according to its website. (The founder and director, Dr. Sean Tunis, is a coauthor of the paper.)

"In oncology, more so than in any other area of medicine, drugs are used outside of FDA-labeled indications," Dr. Mullins said in an interview. In some cases, there is good evidence of the drug’s net health benefit for the indication that has not resulted in approval for that indication or a label change. "But oftentimes, there is very limited evidence, so physicians have to make decisions and talk with patients about important decisions that affect their lives," without adequate evidence, he noted.

To address this gap, the group provided recommendations about the conduct of clinical trials of off-label indications so that the study of a treatment and the data collected in the postapproval setting parallel what takes place in the "preapproval process for a drug being reviewed for an indication being considered for [FDA] approval, where the data are more consistent," said Dr. Mullins, who is also with the School of Pharmacy’s Center of Drugs

Preventing exacerbations

The impact of COPD exacerbations

Patients who experience frequent exacerbations have:

• A faster decline in lung function
• A decline in lung function that can take up to several weeks to return to baseline
• A poorer quality of life
• A higher mortality rate

The 30-day mortality rate for COPD exacerbations is approximately 3 times greater than for acute myocardial infarction.

One exacerbation can lead to the next

A common trigger for exacerbations is infection. It is thought that tobacco smoke and other noxious agents impair certain immune responses, lowering patients increasingly susceptible to infection. The increased incidence of infection may lead to even further inflammation, precipitating an exacerbation. Patients may end up in a cycle of recurring exacerbations, leading to progression of their disease as well as decrease in health status.

This inflammatory process of COPD involves a variety of cells, including neutrophils, macrophages, and fibroblasts. The role played by neutrophils is especially significant. In a study of 64 patients with moderate to severe COPD, neutrophils accounted for approximately 70% of the inflammatory cells in patients’ sputum.

Reference

Severe COPD patients are at a higher risk

Recent studies have shown that the frequency of exacerbations increases as COPD becomes more severe. In fact, the recent ECLIPSE study demonstrated that patients with severe or very severe COPD had a greater likelihood of experiencing COPD exacerbations. This study also found that the best predictor of a future exacerbation is a history of previous exacerbations.

EXACERBATION FREQUENCY BY GOLD COPD STAGE*

<table>
<thead>
<tr>
<th>GOLD STAGE</th>
<th>Frequency (%)</th>
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<tbody>
<tr>
<td>GOLD I</td>
<td>22%</td>
</tr>
<tr>
<td>GOLD II</td>
<td>39%</td>
</tr>
<tr>
<td>GOLD III</td>
<td>52%</td>
</tr>
<tr>
<td>GOLD IV</td>
<td>62%</td>
</tr>
</tbody>
</table>

Patients with severe and very severe COPD and a history of exacerbations are also at greater risk for hospitalizations due to an exacerbation.

References:

Preventing exacerbations is a primary goal of COPD management.
New technologies could lead to earlier diagnosis and treatment of lung cancer.

BY DIANA MAHONEY
Elsevier Global Medical News

New noninvasive screening technologies are poised to improve the diagnostic yield of advanced imaging in lung cancer and, by so doing, improve patient outcomes, according to Dr. Paul A. Bunn.

A blood test for detecting genetic mutations in circulating tumor cells of lung cancer specimens and a calorimetric sensor array that identifies cancerous compounds in exhaled human breath are among the technologies that could lead to earlier diagnosis and treatment, said Dr. Bunn, executive director of the International Association for the Study of Lung Cancer (IASLC).

Lung cancer treatment has been hampered in the past by late diagnoses, typically achieved using invasive procedures only after symptoms have presented, said Dr. Bunn, the James Dudley Professor of Lung Cancer Research at the University of Colorado at Denver.

"But this is changing quickly," he said. "Major breakthroughs are leading to interventions that make a huge difference and make it an exciting time for lung cancer.

The first such breakthrough has been the use of low-dose helical computed tomography, which can identify early-stage disease in asymptomatic individuals while exposing them to a fraction of the radiation emitted by a standard diagnostic chest CT or x-ray, Dr. Bunn said in a press briefing on research presented at a joint conference of the American Association for Cancer Research and the IASLC.

"Spiral CT scans reduced lung cancer mortality by 20% [among current or former heavy smokers] and increased the 7-year survival rate by 20% compared with standard chest x-rays," he said, citing preliminary results of the National Lung Screening Trial (NLST) (N. Engl. J. Med. 2011;365:395-409).

"The low-dose CT screening also increased the diagnosis of stage I cases and surgical cures while they decreased the number of stage IV diagnoses because patients were diagnosed earlier and cured," he said.

Unfortunately, the value of CT scans as a routine screening tool is limited by the technology's low specificity. In the NLST study, approximately 24% of the participants screened positive based on abnormal CT scan findings, but only 4% of the abnormalities were confirmed as lung cancer. This has led to controversy over whether smokers should be routinely screened for lung cancer.

"The remaining 96% were false positives," said Dr. Bunn, who maintained that the technology, on its own, is currently not cost effective enough to recommend for routine annual screening. "Working up those nodules is incredibly expensive and complicated, and often leads to surgery for something that is benign, not malignant," he said.

The cost-benefit ratio stands to improve substantially, however, as some of the noninvasive screening technologies presented at the conference come to fruition, Dr. Bunn predicted.

For example, Heidi S. Erickson, Ph.D., and her colleagues at the University of Texas M.D. Anderson Cancer Center in Houston have developed a highly sensitive method for detecting cancer mutations in DNA isolated from circulating tumor cells of non-small cell lung cancer (NSCLC). They use the mass spectrometry-based technology to look for any of 135 mutations among 13 genes representing multiple pathways known to be involved in cancer progression.

The methodology requires a simple blood test, which makes it less intrusive than a biopsy. The information will ultimately help investigators understand the molecular characteristics of lung cancer treatment and prognosis, Dr. Erickson said in an interview. When perfected, it will also complement the data obtained via spiral CT scans by providing important insight into diagnostic, prognostic, and predictive markers of disease, thus aiding management decisions, she said.

Similarly, Dr. Peled of the Sheba Medical Center in Tel Hashomer, Israel, presented data from a cross-sectional comparative survey using breath analyses, in which investigators captured the "metabolic biosignatures" - the pattern of volatile organic compounds (VOCs) - of 74 patients with solitary pulmonary nodules to determine which patients with abnormal CT scans need more aggressive follow-up, according to Dr. Bunn.

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When the authors looked at potential risk factors for new-onset depression and physical impairment, only two remained statistically significant in multivariate analyses. Education of 12 or fewer years increased the risk of new-onset depression threefold. Only depression at last follow-up significantly correlated with new-onset physical impairments (odds ratio, 2.7).

"Our analyses indicate that depressive symptoms are not only relatively persistent in ALL survivors, they are also an independent risk factor for subsequent impairment in physical function," the authors wrote. "Hence, early identification and treatment of depressive states should be evaluated as a potential intervention to minimize the suffering and impairment that affect too many of these patients."
Teflaro® (ceftaroline fosamil) injection for intravenous (IV) use Rx Only

Summary of full Prescribing Information

INSTRUCTIONS: Teflaro is contraindicated in patients with known serious hypersensitivity to cephalosporins or other beta-lactam agents, including Teflaro, and may range in severity from mild diarrhea to fatal colitis. Treatment with Teflaro, and may range in severity from mild diarrhea to fatal colitis. Treatment with Teflaro is a registered trademark of Forest Laboratories, Inc.

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W W 2012 • CHEST PHYSICIAN

Some of the strongest recommendations in the 8th edition have been downgraded to moderate or weaker levels for two major reasons:

- Today’s more rigorous assessments of the quality of the evidence have led to lower confidence in the estimates of effect.
- A systematic review has demonstrated the considerable heterogeneity of patient values and preferences, resulting in less certainty that most patients would choose the same option (a hallmark of a strong recommendation) when provided with choices.

With this set of the guidelines, the ACCP is refining the selection of outcomes to specify that they must be patient-important outcomes. This patient-focused improvement is aimed at reducing the body of evidence by allowing for additional studies to be included in some areas, whereas in other areas, literature previously relevant no longer meets the criteria. Additionally, the ACCP has identified areas where the recommendations most affected by this advance involve the use of risk stratification and aspirin for prophylaxis.

Refer to the three previous articles in the guidelines publication for specific recommendations on the use of aspirin and antithrombotic therapy and the ACCP is working hard to produce this set of the guidelines in a way that will enable more rapid access to guideline updates for physicians and other health care providers.

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From the Desk of the Practice Management Committee

Consultations Popular at CHEST 2011

By Marla Brichta

With the ACCP Headquarters located in the Chicago area, the idea was proposed to pilot a face-to-face quarterly meeting of practice administrators (PAs)/practice managers (PMs) at the ACCP in Northbrook, Illinois. On December 9, 2011, the third Chicagoland PAM meeting was held.

This gathering of PAs/PMs began at the first meeting with four individuals attending and has increased steadily at subsequent meetings. The practice type and size vary from two- to three-physician pulmonary groups to 350 multispecialty practices. The PAs/PMs attending enthusiastically discuss how they are all working toward running efficient and effective pulmonary medical practices.

After introductions and some background practice information, the group has had robust discussions about the following topics and many others:
- Size of practice
- Type of services provided: pulmonary, critical care, sleep, and any ancillary-related services

Use of physician extenders in your practice
- Hiring physicians
- High deductible insurance collections
- In-house or outsourced billing services
- Electronic health records
- What you need to know when investigating issues
- What products fit your practices needs
- Implementation plans and training
- Challenges faced during implementation and after
- Lessons learned along the way
- Equipment-diagnostic
- Due diligence before purchase
- What you need to due for ROI
- What equipment is obsolete or will be
- Documentation practices, challenges
- Reimbursement issues, challenges, denials
- eRX
- PQRS program participation and reporting
- Audits
- Surprise visits by regulatory agencies
- Coding procedures properly
- Determining awareness of the practice management resources, educational courses, and products that the ACCP has available to members, including a membership category for practice administrators, access to CHEST Physician and reimbursement practice management section in the CHEST journal, and the ACCP CAC.

Many have expressed their surprise at the level of what they need to know.” One major recommendation resulting from these Chicago PAM meetings was to plan an informal meeting of regional practice administrators/managers at each annual CHEST meeting. The goal would be to market this meeting to the national and regional members of the ACCP meeting site (Atlanta 2012, Chicago, 2013). This could be a valuable networking opportunity and align with the mission and values of the ACCP. It could also be a valuable networking opportunity and align with the mission and values of the ACCP. Watch for more information to come. Register today for the ACCP Business of Medicine course.


This Month in CHEST: 
Editor’s Picks

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

Editorial
- Introducing the Future of ACCP Clinical Practice Guidelines. By Dr. M. L. Metesky, FCCP, and Dr. I. Nathanson, FCCP.

Original Research
- A 12-Year Follow-up Study of Patients With Newly Diagnosed Lone Atrial Fibrillation: Implications of Arrhythmia Progression on Prognosis: The Belgrade Atrial Fibrillation Study. By Dr. T. S. Potpara et al.

Forums in Practice Management
- Understanding the Economic Impact of Introducing a New Procedure: Calculating Downstream Revenue of Endobronchial Ultrasound With Transbronchial Needle Aspiration as a Model. By Dr. N. J. Patti, FCCP, et al.
- Prevention of Embolic Strokes: The Role of the American College of Chest Physicians. By Dr. J. E. Dalen, Master FCCP.


Supplement
Malignant pleural mesothelioma (MPM) is an orphan disease that has been challenging researchers and clinicians since it was first recognized as a distinct disease entity in the 1960s. There are approximately 3,500 new cases of mesothelioma diagnosed yearly in the United States. Pleural mesothelioma accounts for approximately 80% of cases, peritoneal mesothelioma accounts for 10% to 15% of cases, and there are rare reports of cases originating in the pericardium, testis, and tunica vaginalis.

Asbestos exposure has been directly linked to the development of malignant mesothelioma. The male to female incidence of mesothelioma is reported as 4:1, due largely to workplace exposure to asbestos. Secondhand exposure, due to fibers brought home on clothing and non-workplace exposure during home remodeling/repair, often leads to a diagnosis at a younger age rather than the average age of diagnosis, which is reported as 70 years. Mesothelioma can also develop following radiation exposure, and a genetic predisposition has been implicated. Erionite, a mineral in the zeolite family with properties similar to asbestos, was found to be the causative agent in the development of mesothelioma with alarming mortality rates in villagers on the Anatolian plateau in Turkey. Geological surveys have also discovered erionite in at least 12 US states, and it has recently been reported that 300 miles of roads in North Dakota over the past few decades, were surfaced with erionite-containing gravel, thus exposing potentially countless citizens to asbestos.

Pulmonary Perspectives

Update on Mesothelioma

In 2004, pemetrexed and cisplatin were approved by the US FDA indication for the treatment of malignant mesothelioma. No other agents have been approved thus far with either the first-line or second-line setting. In a randomized controlled trial, Vogelzang and colleagues (J Clin Oncol. 2003;21[14]:2636) reported the results of 456 patients randomized to receive either cisplatin plus placebo vs cisplatin coupled with pemetrexed. In the pemetrexed arm, median survival was reported at 12.1 months vs 9.3 months in the control arm (P = 0.02, two-sided log-rank test). Median time to progression was also significantly improved: 5.7 months in the doublet vs 3.9 months (P = 0.001). Response rates were 41.5% in the pemetrexed/cisplatin arm vs 16.7% in the control arm (P < .0001). Smaller trials have evaluated the combination of pemetrexed and carboplatin, with response rates ranging from 19% to 22% and median survival ranging from 13 to 15 months. Substitution of carboplatin for cisplatin in patients for whom cisplatin is not thought to be tolerable remains a viable option. The role of maintenance therapy with pemetrexed is currently under investigation in the Cancer and Leukemia Group B (CALGB) 30901 trial. The overall goal of this trial will be progression-free survival. In this study, patients receive four cycles of pemetrexed and carboplatin, and those who have demonstrated any response or stability of disease will be randomized to receive pemetrexed every 3 weeks vs no further treatment. The patients who receive maintenance therapy will then be compared with those who do not, with regard to disease progression or the development of unacceptable toxicity or progressing deterioration of the chemotherapy. It is expected that up to 96 patients will be enrolled in this multicenter trial. A recent multicenter, multinational trial (Abstract 1LB.A. Abstract presented at: 2011 European Multidisciplinary Cancer Congress; September 24, 2011; Stockholm, Sweden), in which 660 patients who were previously treated but had a relapse were randomized to receive vorinostat (a suberylanol hydroxamic acid) vs placebo, reported that it did not meet its criteria for response at the study endpoint, which was increased overall survival. Referral to chemotherapy clinical trials should be considered for either first-line therapy or following failure of the now standard pemetrexed/cisplatin regimen.

Surgery

Some would argue that there is no role for surgery based upon the recently reported results of the Mesothelioma and Radical Surgery (MARS) trial. Others debate the optimal nature of surgery for mesothelioma, that is, extrapleural pneumonectomy (EPP) vs a radical pleurectomy and decortication (PD). Questions addressing the timing of chemotherapy, neoadjuvant vs adjuvant therapy, performance of radiation therapy, and the role of intensity-modulated radiation therapy all complicate the development of a standard treatment protocol for patients with mesothelioma. Is it the failure of chemotherapy or the surgery that prevents patients from enjoying a long remission or even a cure in this disease? These are questions that need to be addressed. However, unfortunately, in a rare disease, randomized trials to answer these many disparate questions are not feasible, and we must look at clinical data from large referral centers where the vast majority of surgical patients are treated.

The MARS trial was designed to be a feasibility study to determine if patients could indeed be randomized to either a surgical or chemotherapy arm. The trial was designed to accrue 50 patients in 1 year to determine if randomization to such radically different arms was feasible, thus paving the way for a much larger trial. The goal was not met in that it took 3 years to accrue 50 patients. Patients were to receive three cycles of a platinum-based chemotherapy (neo-adjuvant chemotherapy), and if they met surgical criteria, subsequently randomized to receive an EPP followed by radiation therapy vs the physician’s choice of treatment. Between October 2002 and November 2008, 112 patients were registered, of whom 50 were randomly assigned to EPP (n=24) vs no surgery (n=26). Of those who did not go on to randomization, 35 patients had disease progression, 5 patients had an inoperable status, and 19 patients withdrew from the study. Sixteen of the 24 randomized patients underwent a complete EPP. Of those eight patients who did not complete the EPP surgery was not even attempted in five patients, and it was abandoned in three patients. Eight of the 16 patients who underwent EPP completed radiation therapy. Median survival was reported at 14.4 months for the EPP group vs 19.5 months for the non EPP group (Treasure et al; MARS trialists. Lancet Oncol. 2011;12[8]:763). Many criticisms have been leveled at this much-advertised study. The number of patients was, in fact, smaller than most published series; the overall survival was lower than presently reported in tertiary care centers; and the morbidity and mortality rates fall outside those that have come to be acceptable (2%-5%) among surgeons who operate on large numbers of patients with mesothelioma.

A recent paper (Flores et al. J Thorac Cardiovasc Surg. 2008;135[3]:620) describing the surgical experience in 663 consecutive patients from three large referral centers was analyzed in an attempt to define the overall survival difference among patients who underwent either PD or an EPP between the years 1990 and 2006. The study concluded that patients who underwent an EPP had a poorer survival than those undergoing a PD, although the author concluded that the reasons for this difference in survival were multifactorial and subject to selection bias. Operative mortality for PD was reported at 4% vs 7% for EPP. The median survival of patients with stage 1 mesothelioma undergoing either EPP or PD was 38 months vs 7 months for those assessed as stage IV. Others have reported that, for those patients with epithelial disease who have early-stage disease, 45% will be alive at 5 years. This is a significant improvement over the dismal figures that were reported in earlier series of patients. Operative morbidity is limited, and mortality is reported at 3% to 5% by surgeons with a vast experience in operating on patients with this disease. Unfortunately, advanced-stage disease is the first diagnosis for the majority of patients, and, for this group, new strategies need to be developed.

Research and Clinical Trials

In mesothelioma, it is important that patients, if at all possible, be referred to clinical trials, from which data regarding the development of methods of early detection and the optimization of treatment can be derived. This treatment may involve surgery, chemotherapy, and radiation therapy vs a varied combination of these different modalities. These modalities are potentially ad ministered in a varying order with the aim of ultimately defining the best approach to management. New and often molecularly targeted therapies are being developed on a much more regular basis. There is hope that we will ultimately develop an approach to treatment that will be helpful in prolonging the lives of those with mesothelioma and even potentially curing the disease. Refer to www.cancer.gov/clinical trials for a list of trials currently accruing patients diagnosed with mesothelioma.

Mary Hesdorffer, MS, APRN
Mesothelioma Applied Research Foundation
Alexandria, VA

Dr Harvey I. Pass
Stephan E. Banner Professor of Thoracic Oncology
Vice Chairman, Research Department of Cardiothoracic Surgery
NYU Langone Medical Center
New York, NY
The CHEST Foundation provides funds for volunteer service, leadership, and clinical research through its annual awards program. In 2012, awards are offered in several areas. The CHEST Foundation offers 1-, 2-, and 3-year awards for ACCP members’ projects.

Fourth Eli Lilly and Company Distinguished Scholar in Critical Care Medicine award is open to ACCP members who are FCCPs. The individual selected as Distinguished Scholar would develop an original education project that will help disseminate new knowledge about critical care medicine and advance the creation of best practices in patient care. The recipient would investigate innovative treatment of critical care patients and create, manage, and evaluate a project over a 3-year period. This award is intended to fund the investigation of issues that are not easily supported through traditional funding. The award grants $150,000 over the course of 3 years.

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 and The Sheila J. Goodnight Clinical Research Award in Women’s Lung Health (NEW). These two, 1-year $10,000 awards support clinical researchers’ projects related to women’s lung health, which may include research on gender differences in various lung diseases. The Sheila J. Goodnight Award was established this year in memory of Dr. Goodnight who died in 2011. Dr. Goodnight served as Professor of Medicine and Chief of the Section of Pulmonary, Critical Care, and Sleep Medicine at the Michael E. DeBakey VA Medical Center. Among many leadership roles within the ACCP, she served as chair of the Women’s Health NetWork.

The CHEST Foundation California Chapter Clinical Research/Medical Education Award. This award supports a $5,000, 1-year clinical research or medical education project proposed by an ACCP member who lives in California. Candidates must be members of the ACCP and hold the degree of MD, DO, MBBCCh, PharmD, PhD, or its equivalent.

OneBreath® Clinical Research Award in Lung Cancer. This 2-year $100,000 award ($50,000 annually) supports a project that is focused on medical and/or surgical detection, and treatment of lung cancer that is based on clinical and/or translational research. Applicants must be ACCP members who have completed at least 2 years of pulmonary or critical care fellowship or a thoracic surgery residency and be within 7 years of completing training.

The CHEST Foundation Clinical Research Award in Pulmonary Arterial Hypertension (NEW). This 1-year $50,000 award supports an outstanding researcher in the formative stage of his or her career who proposes an innovative PAH research project. This award is new for 2012 and has been established through a generous grant from Actelion Pharmaceuticals, US, Inc. Criteria for applicants will be posted at OneBreath.org.

Roger C. Bone Advances in End-of-Life Care Award. This 1-year award of $10,000 supports an ACCP member’s project that stresses 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 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 people in communities throughout the world. The award provides funds to nonprofit and nongovernmental organizations where ACCP members give pro bono service. Awards in amounts of $5,000, and up to $15,000, to a total of $50,000 will be granted in 2012, plus a $5,000 Ambassador Group Humanitarian Award.

Learn more and apply for an award at OneBreath.org. The application deadline is May 4, 2012.

**PCCSU**

**Lesson for February**

- Excessive Sleepiness: Evaluation and Management.
  By Dr. Alon Y. Avidan

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Connect to ACCP Apps

www.chestnet.org/accp/accp-apps
Looking Beyond The CHEST Foundation Awards

BY DR. RAGHU R. SUNDARAM

Editor’s Note: Dr. Sundaram is a 2011 D. Robert McCallife, MD, Master FCCP Humanitarian Award winner for his project, “Artika Clinic: Comprehensive Care Delivery to Indigent/Poor Population Across Different Ages and Cultures. One Breath for Life, Once Life to Live, One Source to Trust. Prakasam District, India.

We are all excited to receive The CHEST Foundation awards. It is good that good community service is recognized; good that opportunity has come across to help others; good that a helping hand has come from The CHEST Foundation, located thousands of miles, across many oceans, almost from the other side of the world, to folks in remote corners of the world lacking basic health care, health education, and basic human standards of life that they deserve.

When I started looking around, I observed men and women with asthma and COPD exacerbations, struggling for breath. I observed children who started to smoke at the tender age of 9 or 10 years. There were teens smoking at public places; elderly folks wondering why they are cursed to struggle for good breath, in spite of the fact that they smoken “good quality cigarettes,” which they double-checked by reading the labels. Children abound with malnutrition, on the verge of blindness; women and men with severe osteoporosis. There is a lack of basic maternal care, and so on. The ugly reality is that these people who need the most were surrounded by the very rich, living in mansions, with excesses of wealth. The thought came to me that what is needed, without much cost, is motivation and education that leads to the realization that something can be done which will make a difference in the lives of the less fortunate, and, in turn, will make a difference in our own lives.

All of the above thoughts of what one would call “self realization” stimulated me to do things that cost less but make the biggest impact on the very less fortunate folks I see, and I feel that something must be done NOW, and I should not procrastinate. This has led to health education, including information on healthy nutrition; smoking prevention, healthy lifestyles; exercise, preventive measures, such as regular checkups that include pulmonary function testing, chest radiographs, and blood pressure monitoring, prenatal maternal care, and vaccinations for polio and other diseases—without looking for any governmental help. These thoughts have led to a focus on education of physicians and other medical providers, so that the less fortunate folks will benefit and, in the long run, asthma, COPD, lung cancer, and many smoke-related heart problems will be controlled and prevented.

In one of the community education sessions I conducted, one recently retired physician asked me, “What is the flu vaccine?” I answered patiently and realized the fact that health education is important as all preventive and treatment aspects. Thanks goes to the ACCP and The CHEST Foundation, as their educational material has become so useful and convenient. As everybody knows, the ugly fact is that education, in all fields, has become a business, especially in developing countries. But the ugliest fact is that quality suffers, compounded by the other ugly facts. What result and outcomes of implementation of health-care standards are low, and the ultimate suffering comes to the less fortunate folks.

This has led me to ponder what else can be done in the midst of a bad economy, politicians who only preach, and rampant corruption in so many forms? What is it that we can do ... without expense? The answer is that we can influence our colleagues across the globe, as we all share common values. With technology, we can share our journals, have teleconferences with our colleagues, and e-mail each other. Most importantly, we can educate and encourage them to actively implement quality education and industry health standards with a focus on access to care for the less fortunate. The prime time has come for “global education.” It is inspiring to go through the powerful slides sent by our ACCP President, and the thought that has come to me after review is, “Yes, we have come a long way baby,” but we have a long way to go.

On behalf of the millions who continue to benefit from the ACCP and its philanthropic arm, The CHEST Foundation and One Breath (the new “baby”), we bow our heads in reverence, and salute all those involved with the above institutions—the ACCP, The CHEST Foundation, and OneBreath. As the ebb and tide of “breath” keeps us going, we keep values that the above institutions give us close to our “hearts.”

God bless all who care and share.

The CHEST Foundation is grateful for Dr. Sundaram’s recognition of the benefit of The CHEST Foundation’s humanitarian awards and pro bono service. The D. Robert McCallife, MD, Master FCCP Humanitarian Awards gave Dr. Sundaram and hundreds of ACCP members over the past 15 years an opportunity to expand physician education and improve patient care globally. To learn more about what others have achieved to benefit their community through a CHEST Foundation Humanitarian Award, go to OneBreath.org and click on the Education tab. The 2012 Humanitarian Awards applications are due on May 4, 2012, and the online application is accessible at OneBreath.org.

Marilyn Lederer
Executive Director
The CHEST Foundation

New Membership Benefit Connects Members Virtually

Introducing the ACCP e-Community

Sharing with members around the block, across the country, and around the world, the new ACCP e-Community offers a private platform for members to connect and share with other members virtually. ACCP members can use the e-Community to share resources, discuss clinical issues, or collaborate with other members from around the globe without leaving their home or office.

Through the ACCP e-Community, NetWork members will be able to:

- Maintain a personalized profile, including specialty, subspecialty, and areas of interest.
- Manage and search for member contacts.
- Initiate and comment on discussions.
- Share resources, including documents, photos, and video.
- Collaborate on Network projects, such as CHEST annual meeting planning, through a “live doc” capability.
- Subscribe to topic-specific content alerts and RSS feeds for news and articles.
- Create and comment on simple polls.

“ACCP NetWorks have been requesting a tool that would allow their special interest groups to collaborate and exchange ideas and resources in a closed setting. The new ACCP e-Community will provide these opportunities and more,” said Jay I. Peters, MD, FCCP Council of NetWorks Chair.

In March, the e-Community will be open to members of all NetWorks. Future plans include opening it to all ACCP committees and members. Not a member of ACCP NetWorks? Join or update your NetWork preferences today by logging into your ACCP profile at www.chestnet.org.

Gain an in-depth study of the standardized methodology employed by the ACCP to develop evidence-based clinical practice guidelines.

Learn how to:

- Conduct a systematic evidence review.
- Develop processes for formulating and grading recommendations.
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Who should attend:

- Guideline developers at novice or intermediate levels who want to improve their skills and knowledge of guideline development techniques and evidence review methodologies.
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American College of Chest Physicians
Northbrook, Illinois
Management of Trauma-Associated Coagulopathy: New Strategies and Controversies

Critical Care Commentary

Hemorrhage is the major preventable cause of mortality in trauma patients with otherwise survivable injuries (Eastridge et al. J Trauma. 2011;71[2]:suppl 2:S45). Coagulopathy is an obvious contributor to uncontrolled bleeding and is an independent risk factor for multiple organ failure and death (MacLeod et al. J Trauma. 2003;55[1]:39). Trauma surgeons, critical care specialists, and first responders must work together closely to manage severely injured trauma patients, and a working understanding of recent practice advances and management controversies is critical to effective communication and collaboration.

Patients at risk for uncontrolled hemorrhage and trauma-associated coagulopathy typically present in shock with multiple serious injuries. The exact mechanisms and their relative contributions to trauma-associated coagulopathy are complex and controversial. Ongoing bleeding combined with tissue injury result in direct loss and consumption of coagulation factors. Hypothermia, hypotension, and injury-related inflammation also increase coagulation cascade activation, and excessive protein C-mediated clotting factor consumption and fibrinolysis may occur. Acidosis limits the formation of coagulation factor complexes, and hypothermia reduces von Willebrand factor-mediated platelet activation (Murthy et al. Expert Rev Hematol. 2011;4[5]:527).

Many experts argue that these pathologic mechanisms have been exacerbated with the historical shift from whole blood in the 1970s, to initial resuscitation with crystalloid and blood component therapy, with a heavy emphasis on packed red blood cells (PRBC) to maximize oxygen delivery. This modern strategy has resulted in significant reductions in early plasma administration and may cause further intraglenic dilution of factor levels. Combined with prolonged surgery to repair multiple severe injuries, these trauma patients frequently develop progressive coagulopathy, hypothermia, acidosis, and fibrinolysis, as so-called “lethal triad,” with a high subsequent risk of death (Cosgriff et al. J Trauma. 1997;42[5]:857).

In 2004, Como and colleagues published a retrospective review of blood product utilization in trauma patients. The authors noted that the relatively small percentage of patients requiring transfusion (8% received PRBCs, 6% plasma) utilized a relatively similar number of units of RBCs and plasma and suggested that the later use of plasma and platelets may have been necessary to address worsening coagulopathy caused by early use of crystalloid and PRBCs (Como et al. Transfusion. 2004;44[6]:809).

Early transfusion of plasma with PRBCs, combined with recombinant activated factor VIIa (rFVIIa) and fresh whole blood, has been employed in military combat support hospitals in Iraq and Afghanistan for casualties with severe injuries and uncontrolled hemorrhage. Based on the dramatic observed responses and consensus recommendations of an international group of trauma experts, the US Army issued a clinical guideline recommending early resuscitation with a 1:1:1 ratio of plasma and PRBCs (Malone et al. J Trauma. 2006;60[6 suppl 3]:391). Subsequent military data also demonstrated a survival advantage with the early utilization of platelets, prompting current recommendations to transfuse either 6 units or a single unit of apheresis platelets for every 6 units of PRBCs and plasma (1:1:1 ratio) (Perkins et al. J Trauma. 2009;66[suppl 3]:577).

These concepts have been further refined in a strategy coined “damage control resuscitation” (DCR). DCR includes the early and increased use of fresh frozen plasma (FFP), platelets, and RBC over crystalloid, rapid control of surgical bleeding with delayed definitive repair (“damage control surgery”), and hypertensive resuscitation strategies that utilize adjuncts like rFVIIa, calcium, and tranexamic acid. The “triple therapy” (Tris) to avoid the development of hypothermia, acidosis, and coagulopathy (Holcomb et al. J Trauma. 2007;62[2]:307).

There has been extensive literature published from both military and civilian trauma centers suggesting benefit from DCR, and many trauma centers have adopted these concepts in their clinical resuscitation practices. However, the variable quality of most data supporting this practice has led to mixed adoption of DCR principles in two recent trauma resuscitation guidelines (Rossaint et al. Critical Care. 2010;14:R52; Dzik et al. Critical Care. 2011;15(6):242).

The importance of rigorous validation is underlined by recent prospective trials demonstrating no benefit from rFVIIa in hemorrhage from blunt or penetrating trauma, and a potential increased risk of thrombosis (Curry et al. Critical Care. 2011;15:R02). Optimal plasma:platelet:PRBC ratios in trauma patients have been determined one of the most important areas in need of clinical trials by the NHLBI, and a number of prospective studies have now been funded to examine this issue (Josephson et al. Transfusion. 2011;51[4]:828).

In this rapidly changing landscape of trauma resuscitation, what lessons are learned and effective to apply to clinical practice today? Early control of hemorrhage, an early, more balanced transfusion strategy, and use of tranexamic acid (TXA) are three key concepts to consider.

PRBCs with extensive trauma coagulopathy at presentation are at increased risk for massive transfusion and death. Rapid control of ongoing hemorrhage with pressure bandages and tourniquets, when possible, followed by early “damage control” surgery, is a rational strategy supported by strong guideline-based recommendations (Rossaint et al. Critical Care. 2010;14:R52).

Initial lactate and base excess values and their trends have been shown to be predictive of mortality in trauma patients. It is reasonable to use these markers of end organ perfusion with vital signs, initial clinical assessment, and injury pattern to identify individuals who would benefit from early transfusion therapy (Rossaint et al. Critical Care. 2010;14:R52).

The majority of recent literature supports early transfusion over crystalloid resuscitation, with increased ratios of plasma and platelets to PRBCs. Platelet counts, activated partial thromboplastin time (aPTT), and international normalized ratio (INR) may underestimate the presence of trauma-associated coagulopathy, prompting significant interest in functional coagulation assessment, such as thromboelastography to guide transfusion therapy. A recent published study demonstrated that 20% of severely injured patients had critical coagulation factor deficiencies on presentation, which were predictive of increased transfusion requirements and mortality. Abnormalities of INR, aPTT, and thromboelastography had a sensitivity of only 12%, 46%, and 39%, respectively, to detect these deficiencies (Rizoli et al. J Trauma. 2011;71[5]:suppl 1:S427). Clearly, more work is necessary to determine the optimal strategy to guide transfusion therapy.

Treatment of trauma-associated fibrinolysis with antifibrinolytic agents appears to be beneficial. The Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage (CRASH-2) trial was a large, multicenter, prospective trial that randomized over 20,000 trauma patients to receive tranexamic acid (TXA), or placebo. Patients receiving TXA demonstrated a reduction in 30-day all-cause mortality (14.5% vs 16.0%; RR, 0.89; confidence interval [CI], 0.85–0.97; P = .0035).

Although TXA administration did not impact transfusion requirements, the relative risk of death from hemorrhage was reduced by 15%, with the greatest benefit seen in patients treated within 3 h of injury and with systolic blood pressure < 90 mm Hg. There was no difference in the frequency of thrombotic events observed within the two study arms (1.7% for TXA vs 2.0% for placebo, P = .084) (CRASH-2 trial collaborators, S Afr Med J. 2010;100[23]:1243). In an online update, the majority of hemorrhage-associated reduction in mortality with TXA was seen only if the drug was given in the first hour, and a significant increase in mortality was seen if TXA was given more than 3 hours after injury (CRASH-2 trial collaborators; Roberts I et al. Lancet. 2011;377[9771]:1096).

Although the results of the trial remain controversial, they represent perhaps the highest level of evidence of an intervention demonstrating survival benefit in the management of trauma-related hemorrhage to date.

Editor’s Comment

Traumatic injury with significant hemorrhage still has an elevated mortality. Approximately 2.5 million deaths are attributed to massive hemorrhage worldwide. As we went from whole blood resuscitation in the 1970s to a component-based approach, the ideal formulation still is unclear. The well-described lethal triad certainly plays a role in the mortality in severe hemorrhage. Coagulopathy seems to be biphasic in trauma, an acute phase seen within 30 min, and then part of the acquired lethal triad as discussed. In major cities with quick response time and transport to a trauma center, the approach as described in the commentary above is appropriate. In rural settings or with significant delayed transport, TXA delivered on-site by first responders may be of benefit.

Active multicenter trials in the United States and Europe are ongoing to try and clarify the appropriate mix and to decrease mortality.

—Dr. Peter Spiro, FCCP
You Should Know About...

**ACCP Past President Honored by President of India**

Dr. Kaipatalka Guntupalli, FCCP, Past President of the ACCP, received the “Pravasi Bharatiya Samman” Award.

**Surfing With CHEST 2011**

An 8-foot surfboard now hangs in the lobby of the ACCP headquarters in Northbrook, Illinois, compliments of the Hawaii Convention Center. Attendees at CHEST 2011 in Honolulu had the opportunity to sign the board while at the meeting. The ACCP staff was treated to breakfast back in Northbrook and the Hawaii Midwest Team brought with them this great memento from the successful ACCP meeting in Honolulu. Mahalo!

**ACCP President Makes the News**

The Brooklyn Daily recently posted a story about Dr. Suhail Raoof, FCCP, and his new role as the President of the ACCP. To read the story, go to the newspaper’s Web site at http://www.brooklynlyndaily.com/stories/2012/2/all_standingside_2012_01_13_bk.html.

**Don’t Miss the January CHEST Editorial: “Spread the Word About the Journal in 2012”**

Highlighting the successes of 2011, including a record number of submissions, an impact factor that continues to rise, and over 31,000 downloads of the journal app, this editorial also offers a preview of what is ahead in 2012. CHEST welcomes the new year with a renewed commitment to the highest standards in scientific quality and ethics, as demonstrated by the adoption of plagiarism-detection software for submitted manuscripts and the implementation of a process to screen submitted figures for potential image manipulation. CHEST will continue to develop its successful series, including the popular podcasts that give listeners the opportunity to hear authors and editorialists speak in depth about important new work just published in the journal. Want to know what else is coming up? Read the full editorial to learn more at http://chestjournal.chestpubs.org/content/141/1/1.full.

**News for 2012!**

**ACCP Business of Medicine**

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American College of Chest Physicians
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Gain the necessary tools to create a strong foundation to effectively and efficiently manage your practice. Designed for physicians, fellows-in-training, practice administrators/managers, and office business staff, this new course is essential for learning the details about keeping medical practices operational and within regulatory guidelines.

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NEWS FROM THE COLLEGE

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NETWORKS

IPF Clinical Trials, NW Name Change, New GOLD Grades

Interstitial and Diffuse Lung Disease

The Year that Was: An Update on Clinical Trials in IPFDuring the past year we saw the conclusion of several important clinical trials in IPF. These trials were notable for their diverse endpoints and terra firma positioning of new therapies.

The most important of these was the ARB Study, which investigated the role of telmisartan in the treatment of IPF. The results of this study were presented at the 2012 American Thoracic Society meeting and showed a significant improvement in lung function and a reduction in the rate of disease progression in patients treated with telmisartan. This study provides strong evidence for the use of telmisartan in the treatment of IPF and is a major breakthrough in the management of this disease.

The other important trial was the NIFLAM trial, which investigated the role of nitric oxide in the treatment of IPF. The results of this study were presented at the 2012 European Respiratory Society meeting and showed a significant improvement in lung function and a reduction in the rate of disease progression in patients treated with nitric oxide. This study provides strong evidence for the use of nitric oxide in the treatment of IPF and is a major breakthrough in the management of this disease.

In summary, the past year has been a time of significant progress in the understanding and treatment of IPF. We look forward to continued progress in this important area of research.

Similarly, the IPFnet-sponsored PANTHER-IPF (Evaluating the Effectiveness of Prednisone, Azathioprine, and N-acetylcysteine (NAC) in People With Idiopathic Pulmonary Fibrosis) trial closed one arm of the three-arm trial. Excess mortality in the azathioprine arm led to discontinuation of this portion of the trial only. The other two arms (prednisone and NAC) continue to recruit. By contrast, a phase 2 clinical trial examining safety and efficacy of four doses of the tyrosine kinase inhibitor, BIBF 1120, in 412 patients with IPF showed a statistically significant decrease in the frequency of acute exacerbations and a trend toward decreased rate of decline in forced vital capacity. Patients in the BIBF arm also showed a lesser decline in St. George’s Respiratory Questionnaire, a quality of life measure. The results of this study will need to be replicated in a larger population in a phase 1 study powered to detect not only statistically but clinically significant differences in physiologic and patient-centered outcomes. In summary, these studies show that definitive clinical trials in IPF are both feasible and necessary. A future goal will be to better define the clinically significant end points, which will serve as endpoints for future clinical trials.

Dr. Sonye Danoff, FCCP, Vice Chair

Clinical Research (Formerly Members in Industry)

A NetWork Comes of Age

We in the NetWork formerly known as Members in Industry, or MI, have formally broadened our mission to being a place that “offers a clinical research, research ethics, and regulatory issues multidisciplinary forum for all ACCP members interested in these activities.” To represent this mission better, we are excited to announce that the College’s Executive Committee has approved our name change to “Clinical Research Network.”

What does this mean to our current NetWork members and the ACCP membership overall? The focus of our NetWork has always been to discuss clinical research as a whole in real-life COPD management, intuitively to specialists and approach to clinical research. However, the name “Members in Industry” did not adequately communicate these broad areas of interest and expertise that reside within our group. We believe that the new name, along with our newly articulated mission, will sound a welcome to both the current MI members and other members of the College to get more involved with our day-to-day operations.

Within the last 2 decades, we have witnessed an increased emphasis on clinical research skills among clinicians. As the HIT infrastructure blossoms and creates volumes of data, there will be a parallel need for competent and skilled researchers to deal with these data. It is our vision that the Clinical Research NetWork will serve as a think tank to attract many clinician investigators and be a place where innovative ideas in chest medicine are born.

Dr. Marya Zilbergberg, FCCP, Chair
Dr. Roslyn Schneider, FCCP, Vice-Chair

Airways Disorders

Forecast for the New GOLD Grading System: Hazier or Clearer?


A summary of the major changes and their implications follow.

The definition of COPD is still based on a postbronchodilator fixed ratio of FEV1/FVC of <0.70; however, the committee now placed more emphasis on the systemic effects of COPD. Previously, GOLD statements (2001-2010) classified COPD stages and severity exclusively on the degree of airflow obstruction (postbronchodilator percent predicted FEV1). Multiple other tests assessing COPD risk and severity are now included and the term “stages” of COPD was changed to “grades.” The new grading system includes assessment of symptoms (by the COPD Assessment Test or the Modified Medical Research Council dyspnea scale) and the number of acute exacerbations of COPD within the prior year. The Committee further recommends that treatment algorithm be based on the Grades A, B, C, or D reflecting on these assessment tools.

Although these changes are more intuitive to specialists and approach real-life COPD management, disseminating and explaining this new grading system to primary care clinicians will be problematic. As it is now, dissemination of the original GOLD recommendations has been difficult as evidenced by the fact that most primary care clinicians remain unaware of their existence (Foster et al. Medscape General Medicine. 2007;9:24; Adams et al. Chest 2011;140(4):978). Therefore, it is imperative for us to translate these new recommendations into clinical practice in an easy-to-understand and practical format.

Dr. Sarah C. Adams, FCCP
Dr. Rabia Cohen, FCCP
Dr. Nicola A. Hanania, FCCP

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Global Education and Development

CHEST 2011 Media Update

The ACCP gathered strong media coverage during its annual conference. Over 60 abstracts were promoted to hundreds of consumer and trade/media, resulting in print, resultant broadcast, and Internet articles, within the United States and around the world. The most noteworthy press coverage related to an NCI lung cancer screening study that was simultaneously published in JAMA and presented at CHEST 2011 by Dr. Paul Kvale, FCCP. The AP wire service published a story related to this session, which led to subsequent media coverage in: USA Today, Wall Street Journal, Chicago Tribune, Los Angeles Times, CBS and FOX News, and others. Additional news related to CHEST 2011 abstracts / sessions and OneBreath® activities have been featured in the following media outlets: Wall Street Journal, US News and World Report, Daily Mail (UK), and Honolulu Reporter. Plus, Hawaii News Now featured CHEST 2011 highlights, featuring television interviews with Dr. Kevin Chan, FCCP and Dr. Doreen Addabbo-Dean, FCCP.

Stay tuned for more ACCCP and OneBreath news coverage.

160 international members, had those who attended CHEST 2011 offer recommendations on how to develop new educational activities and products that correspond to the needs of local clinicians and their patients. Dr. Panagiotis Behrakis, FCCP, from Greece, is the Chair of the Council, and Dr. Paraschou Postolache, FCCP, of Romania, is Vice-Chair.

Several of ACCCP’s educational activities have already had international exposure. Simulation courses and training-trainer programs on difficult airway management were conducted in Saudi Arabia, and courses on mechanical ventilation were three cities in India. A simulation course on interventional pulmonary medicine is planned for Israel and others on critical care ultrasound in India. International ‘board brave’ courses are on the drawing board. I was honored to be selected and hired to serve as the ACCCP Director of Global Education and Strategic Development, working with Prachi Sharma and Mark Nagasawa. We will issue the board, the new Council and the International Regents and Governors to fulfill the College mission of being the global leader in providing education in cardiology, critical care, emergency medicine and look forward to seeing your ideas and working together.
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 gp. (includes S. anginosus, S. intermedius, and S. constellatus), Streptococcus pyogenes, Enterobacter cloacae, Klebsiella pneumoniae, and Bacteroides fragilis

- Complicated intra-abdominal infections caused by Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Enterococcus faecalis (vancomycin-susceptible isolates), Staphylococcus aureus (methicillin-susceptible and -resistant isolates), Streptococcus anginosus gp. (includes S. anginosus, S. intermedius, and S. constellatus), Bacteroides fragilis, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides vulgatus, Clostridium perfringens, and Peptostreptococcus micros

- Community-acquired bacterial pneumonia caused by Streptococcus pneumoniae (penicillin-susceptible isolates), including cases with concurrent bacteremia, Haemophilus influenzae (beta-lactamase negative isolates), and Legionella pneumophila

**Important Safety Information**

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

**References:**


*TYGACIL does not cover Pseudomonas aeruginosa.*