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CHEST Physician

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High-risk COPD patients had significantly fewer exacerbations when the macrolide antibiotic was added to standard treatment.

Daily Azithromycin Cut Acute COPD Events

BY MIRIAM E. TUCKER
Elsevier Global Medical News

DENVER – The addition of daily azithromycin to standard treatment reduced the frequency of chronic obstructive pulmonary disease exacerbations and improved quality of life at 1 year in a large, prospective, randomized, placebo-controlled clinical trial that included more than 1,100 high-risk COPD patients.

Use of the macrolide antibiotic was associated with a significantly greater incidence of hearing decrement, although the overall rate was low and tended to reverse when the drug was stopped, Dr. Richard K. Albert, FCCP, reported at an international conference of the American Thoracic Society.

Macrolide antibiotics have antimicrobial and immunomodulary effects, and chronic administration has been associated with improvements in other inflammatory lung conditions, such as cystic fibrosis. However, previous studies that examined the use of macrolides in COPD have produced conflicting results, with five studies showing improvements and two failing to demonstrate a benefit. These studies have all been small – the largest included only 109 patients – and all had study-design problems, said Dr. Albert, professor of medicine at the University of Colorado at Denver, and chief of medicine at Denver Health.

Dr. Albert and his colleagues enrolled 1,142 patients with moderate to severe COPD who were at increased risk for acute exacerbations based on having received supplemental oxygen within the previous year, a history of receiving systemic corticosteroids, and/or a history of hospitalization or an emergency department visit for a COPD exacerbation within the past year.

Patients with asthma, bronchiectasis, hepatic or renal insufficiency, resting tachycardia, prolonged QTc intervals, or audiometric abnormalities were excluded.

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House Hears SGR Alternatives, Vows Action

Panel calls for physician-led plan.

BY FRANCES CORREA
Elsevier Global Medical News

WASHINGTON – A plan to finally replace Medicare's much maligned sustainable growth rate payment formula could be unveiled this summer, federal lawmakers predicted at a committee hearing.

"Here's the bottom line: If we get to December and we're doing an extension, that's a failure on our part," Rep. Michael Burgess (R-Tex.) said at the hearing of the House Energy and Commerce Committee's Subcommittee on Health. "We need a permanent solution that's predictable, updatable, and reasonable for this year – and nothing else will do."

"Whatever virtues the SGR had when it was created 14 years ago … it's clear that they have vanished," noted Rep. Henry A. Waxman (D-Calif.). He added that in the past 2 years, Congress has had to pass legislation six times, blocking fee cuts of up to 21% or more.

Approximately 30 medical associations responded to the House subcommittee's request for suggestions and proposals in developing a new system. Speaking with a five-person panel of experts from medical associations and health policy organizations, House subcommittee members considered alternatives to the current SGR formula, which some participants labeled as anything but sustainable.

One Size Won't Fit All

While the details of the plans vary, they do show a consensus on several fronts: repealing the SGR, moving away from the traditional fee-for-services model, and having a 4- to 5-year transition period in which providers can experiment with a variety of payment systems.

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INSIDE

Diaphragmatic Hernia Survivors Do Well

BY DAMIAN McNAMARA
Elsevier Global Medical News

FORT LAUDERDALE, FLA. – More children are achieving long-term survival following repair of a congenital diaphragmatic hernia, but "this new group of survivors does not appear to have much greater sequelae," Dr. Melinda Solomon said.

For example, despite early pulmonary hypertension and decreased pulmonary artery size, their cardiac function tends to be normal in adulthood. Exercise impairments tend to be mild as well, Dr. Solomon said at a seminar on pediatric pulmonology sponsored by the American College of Chest Physicians and the American Academy of Pediatrics.

"The issue used to be: Can we get these patients to survive and make it to adulthood?" Dr. Solomon said.

They are not entirely free of adverse sequelae, however; obstructive findings and the incidence of asthmalike symptoms can be significantly increased in this population, according to

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Add-On Therapy for COPD

Azithromycin • *from page 1*

The high-risk patient population enrolled in the study represents about a third of all patients with COPD, Dr. Albert noted.

The patients were randomized to receive azithromycin (250 mg/day) or placebo along with usual treatment for 1 year. They had a mean age of 65 years, 41% were women, and 82% were white. They had postbudesonide FEV_1 of 1.1 mL, FEV_1 about 40% of predicted, and an FEV_1/FVC ratio of 42%. All had a history of smoking, with an average of about 55 pack-years, and about one-fifth were current smokers. The majority (85%) had received systemic corticosteroids for an acute exacerbation of COPD (AECOPD) in the past year, three-quarters were taking long-acting beta-agonists (LABAs) and/or inhaled corticosteroids, and about two-thirds were on long-acting muscarinic antagonists (LAMAs).

In all, 1,117 patients (558 azithromycin and 559 placebo) were included in the intent-to-treat analysis, and 996 (494 azithromycin and 502 placebo) were actually evaluated at 1 year.

The primary end point (the median time to first AECOPD) was 266 days for the azithromycin group, compared with 174 days for those taking placebo, a statistically significant difference (hazard ratio, 0.73).

A secondary end point (the rate of AECOPD) was 1.48 per patient-year for azithromycin vs. 1.83 per patient-year for placebo, again highly statistically significant, Dr. Albert said. Improvements seen with azithromycin over placebo were significant, despite the fact that most patients were taking inhaled corticosteroids, LAMAs, and/or LABAs, he noted.

There were trends for reductions in all-cause and COPD-related hospitalizations, as well as emergency department and urgent care visits with azithromycin, but these were not statistically significant. There was a slightly significant difference in frequency of unscheduled office visits favoring the azithromycin group. A reduction in intubation was also seen with azithromycin, but the numbers weren't large enough to reach significance.

On the St. George's Respiratory Questionnaire, a self-completed questionnaire for measuring impaired health and perceived well-being in patients with airway diseases (Respir. Med. 1991; 85[suppl. B]:25-31; discussion 33-7), the azithromycin group had a drop in its score by 2.8 units at 1 year, compared with just 0.6 units for placebo, also highly statistically significant.

The frequency of serious, nonfatal adverse events including pneumonia, neoplasm, gastrointestinal tract problems, QT prolongation, or other cardiovascular problems did not differ significantly between the two groups.

Fatal serious adverse events also did not differ, although there were slightly more neoplasms in the placebo group. Adverse events leading to drug discontinuation also did not differ, he said.

However, the measured hearing decrement was significantly more common in the azithromycin group, occurring in 142 (25%) vs. 110 (20%) of the placebo group. The mean change in hearing in decibels was small (0.7 dB), compared with no change in the placebo group at 3 months, with no significant difference at 12 months.

Data suggested the audiometry used to assess hearing may have overestimated the degree of hearing decrement. Of 80 azithromycin patients who had hearing decrements detected prior to the 12-month study evaluation, investigators stopped the drug in 61. Of those, hearing returned to normal in 21 patients.

THE MEDIAN TIME TO FIRST ACUTE EXACERBATION WAS 266 DAYS FOR THE AZITHROMYCIN GROUP, COMPARED WITH 174 DAYS FOR THOSE ON PLACEBO.

Of the 19 patients for whom the azithromycin wasn't stopped, hearing returned to normal in 6 patients.

Similarly, of 45 placebo patients with hearing decrements detected prior to 12 months, placebo was stopped in 37 and hearing returned to normal in 14. Of eight patients who continued taking the placebo, hearing returned in two.

"While we believe there are differences in the frequency with which azithromycin causes hearing disorders, we think we have overestimated that frequency in both groups," Dr. Albert said.

At enrollment, 14% of the azithromycin and 15% of the placebo group were colonized with selected respiratory pathogens.

Excluding those patients colonized with selected respiratory pathogens at enrollment, 12% of the azithromycin group became colonized with respiratory flora during the study, compared with 28% of the placebo group at the 12-month assessment, a highly significant difference.

Colonization with macrolide-resistant pathogens did not differ between the groups at baseline. However, during the study, 47 (81% of those who had culture obtained) in the azithromycin group had become colonized with macrolide-resistant pathogens, compared with 108 (47% of those cultured) in the placebo group. No association was found between colonization and pneumonia, he said.

The study was funded by the National Heart, Lung, and Blood Institute. Dr. Albert stated that he had no relevant disclosures. ■

COMMENTARY

Dr. Darcy Marciniuk, FCCP, comments: Daily azithromycin therapy significantly decreased exacerbation frequency and lengthened the time to first COPD exacerbation in this prospective 1-year trial undertaken in high-risk moderate-severe COPD patients. It is interesting that a measured hearing loss was noted more frequently in the azithromycin group that frequently resolved with the discontinuation of therapy. Colonization with macrolide-resistant organisms also occurred more frequently in the azithromycin group but was not associated with pneumonia. This therapy may be an effective option in COPD patients at high risk for repeated exacerbations, but a baseline hearing assessment coupled with regular surveillance would be prudent.

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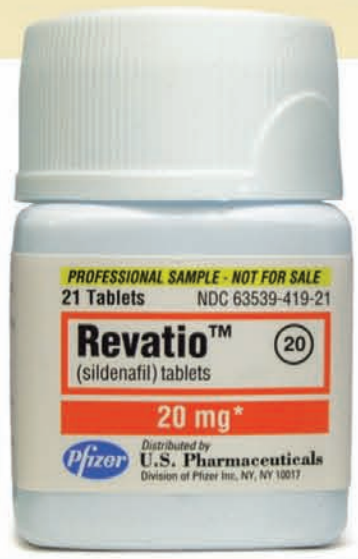

Important Safety Information

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

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

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

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

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

Non-arteritic anterior ischemic optic neuropathy (NAION) has been reported post-marketing in temporal association with the use of PDE5 inhibitors for the treatment of erectile dysfunction, including sildenafil.

It is not possible to determine if these events are related to PDE5 inhibitors or to other factors. Physicians should advise patients to seek immediate medical attention in the event of sudden loss of vision while taking PDE5 inhibitors, including REVATIO.

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

REVATIO should be used with caution in patients with anatomical deformation of the penis or patients who have conditions which may predispose them to priapism.

The effectiveness of REVATIO in pulmonary hypertension (PH) secondary to sickle cell anemia has not been established. In a small, prematurely terminated study of patients with PH secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported by patients who received REVATIO than by those randomized to placebo.

REVATIO contains sildenafil, the same active ingredient found in VIAGRA®. Combinations of REVATIO with VIAGRA or other PDE5 inhibitors have not been studied. Patients taking REVATIO should not take VIAGRA or other PDE5 inhibitors.

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

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

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

Indication

REVATIO is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise ability and delay clinical worsening. Delay in clinical worsening was demonstrated when REVATIO was added to background epoprostenol therapy. Studies establishing effectiveness included predominantly patients with NYHA Functional Class II-III symptoms and etiologies of primary pulmonary hypertension (71%) or pulmonary hypertension associated with connective tissue disease (25%). The efficacy of REVATIO has not been adequately evaluated in patients taking bosentan concurrently.

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Diaphragmatic Hernia Repair Avoids Worse Outcomes

BY MARK S. LESNEY
Elsevier Global Medical News

PHILADELPHIA – According to a lifetime risk analysis based on mortality data, elective repair of diaphragmatic hernia is associated with a favorable risk-benefit profile for patients in their 50s, 60s, and perhaps even early 70s.

"This analysis suggests the practice of repair of uncomplicated diaphragmatic hernia may avoid the morbidity and mortality associated with either obstruction or gangrene," said Dr. Subroto Paul, FCCP, and his colleagues at Cornell University in New York.

Current clinical practice is to repair symptomatic diaphragmatic hernias to avoid complications such as obstruction or gangrene. However, practice patterns are based largely on limited data from institutional case series, according to Dr. Paul and colleagues.

Mortality was significantly higher in patients with uncomplicated hernia who went on to readmission with obstruction or gangrene, Dr. Paul said at the annual meeting of the American Association for Thoracic Surgery, where he presented an analysis of the National Inpatient Sample (NIS) database.

Over a 10-year-period, 193,554 patient admissions were identified for the primary diagnosis of diaphragmatic hernia of any type. An uncomplicated diaphragmatic hernia was the diagnosis in 161,777 (83.6%) admissions. Of these, 38,764 (24.0%) patients underwent an elective repair of their hernia as the principal procedure for their admission.

A diagnosis of diaphragmatic hernia with obstruction or gangrene was the reason for admission in 31,127 (16.1%) and 651 (0.3%) patients, respectively. Mortality was significantly higher in patients who were admitted with obstruction or gangrene (4.5% vs. 27.5%, respectively), compared with patients

who were admitted for an elective hernia repair (1%).

Morbidity from pneumonia and sepsis was also significantly higher in patients admitted for obstruction or gangrene. Symptomatic admission was associated with more intensive hospitalization, as evidenced by significantly increasing length of stay – 6 days (uncomplicated) vs. 9 days (obstruction) vs. 17.5 days (gangrene) – and the need for mechanical ventilation (3.6% vs. 9.7% vs. 41.3%, respectively).

Dr. Paul reported that he had no relevant disclosures. ■

COMMENTARY

Dr. Richard Fischel, FCCP, comments: The data clearly show the advantages for elective repair vs. emergent repair. It would be interesting to know if the patients admitted with a diagnosis of obstruction or gangrene had prior knowledge of their diaphragmatic hernias. If so, they can now be offered the recommendation to have an elective repair and avoid the risks of emergent surgery.

Obstructive Disease Common

Hernia • *from page 1*

long-term follow-up studies. Recurrence of the hernia is also a lifelong concern, said Dr. Solomon of the division of respiratory medicine at the Hospital for Sick Children in Toronto.

In a long-term follow-up study done in the Netherlands, mean forced expiratory volume in 1 second (FEV_1) was significantly lower among 53 survivors at –1.63, compared with 0.08 among controls (Eur. J. Respir. 2009;34:1140-7). "Prebronchodilatation, the FEV_1 was below the lower limit of normal in 46% of patients but not in controls," Dr. Solomon said. The residual volume/total lung capacity (RV/TLC) ratio exceeded the upper limit of normal in 52% of affected children and in none of the controls, a significant difference.

The same study did not reveal a difference in exercise performance between groups. "This is good news" that children with congenital diaphragmatic hernia can have normal exercise capacity in adulthood, Dr. Solomon said.

All cardiac indexes from exercise testing were within the normal range in another follow-up study of 23 children and 23 case-matched controls at the Hospital for Sick Children (Pediatr. Pulmonol. 2006;41:522-9).

Echocardiography revealed that "they actually had very good myocardial function but, as expected, a smaller pulmonary artery on the affected side," Dr. Solomon said. Pulmonary function testing revealed abnormalities even 10-16 years after treatment, she added, but FEV_1 was in the normal range. For example, mean FEV_1 as percent predicted was 83% in patients versus 98% in controls; mean RV/TLC ratio was 31% in patients versus 22% in controls.

Some degree of obstructive disease is common among survivors. Airway hyperactivity with asthmalike symptoms, for example, can last well into adulthood, Dr. Solomon said. It is sometimes difficult to determine who should be prescribed bronchodilators, she added. The 2009 study in the Netherlands found that 28% of affected children responded to these agents, compared with 6% of controls.

Musculoskeletal abnormalities such as scoliosis, pectus excavatum, and chest wall asymmetry develop in almost one-third of patients, Dr. Solomon said. "This often bothers the family as the respiratory issues resolve. It's important to warn them in advance."

Long-term neurocognitive function remains unclear, and sensorineural hearing loss and its association with congenital diaphragmatic hernia are controversial (Int. J. Pediatr. Otorhinolaryngol. 2010;74:1176-9). Because such hearing loss occurs both in those who undergo extracorporeal membrane oxygenation and in those who don't, the underlying etiology remains unknown, she said.

Another unanswered question is whether patch repair or video-assisted thoracic surgery (VATS) yields better long-term outcomes, Dr. Solomon said. Although many studies in the literature point to a higher recurrence rate with patch repairs, at her institution, "VATS has a much higher incidence of recurrence."

Congenital diaphragmatic hernia occurs in about 1 in every 3,000 live births. About 85% are left sided, the classic posterolateral Bochdalek hernia. Comorbidities affect approximately 40%-50% of these children; congenital heart disease, in particular, is associated with an increased risk of mortality.

She had no relevant disclosures. ■

Elimination of Tobacco Use Deemed No. 1 Priority

United Nations High-Level Meeting will focus world attention on tobacco reduction.

BY MIRIAM E. TUCKER
Elsevier Global Medical News

Near-elimination of tobacco consumption worldwide by 2040 was proposed as the No. 1 priority for this fall's United Nations High-Level Meeting on Noncommunicable Disease in a joint statement from two stakeholder coalitions.

Specifically, the authors proposed goals of reducing worldwide tobacco consumption to less than 5% by the year 2040. "We propose a goal to achieve a world essentially free from tobacco by 2040," they said.

Dietary salt reduction, improved diet and physical activity, reduction in hazardous alcohol intake, and universal access to essential drugs and technologies were also listed as top global NCD priorities by the Lancet NCD Action Group, an informal collaboration of academics, practitioners, civil society organizations, and the NCD Alliance (www.ncdalliance.org), comprising four international nongovernmental organizations (Union for International Cancer Control, International Union Against Tuberculosis and Lung Disease, International Diabetes Federation, and World Heart Federation).

The five priorities were chosen because there is good evidence for each regarding their substantial impact on health and cost effectiveness, the low cost of implementation, and financial feasibility for scale-up.

The UN High-Level Meeting (UN HLM) on NCDs in September 2011 is expected to focus the world's attention on NCDs in the same way that a similar meeting did for HIV/AIDS in 2001, which concluded that dealing with the disease was central to the world development agenda. The rising global epidemic of NCDs is now responsible for two-thirds of all deaths worldwide and has become a major barrier to development, according to Dr. Robert Beaglehole of the University of Auckland, New Zealand, and 43 coauthors representing the two umbrella groups (Lancet 2011 [doi:10.1016/S0140-6736(11)60393-0]).

"The UN HLM is a turning point in the way we approach global health issues, and it will place NCDs on the development agenda. The global community has to take this opportunity and sustain the momentum to achieve the goal of avoiding premature NCD deaths and disability, thus improving global health in the years to come," the authors wrote.

Tobacco reduction would be accomplished via full implementation of the 2003 World Health Organization Framework Convention on Tobacco Control, which calls for reducing demand for tobacco via methods such as raising tobacco taxes, legislation of health warnings, and smoking prohibitions. Salt reduction would be accomplished via mass-media campaigns and voluntary reformulation of food products by industry.

Using those methods, the yearly cost to implement tobacco control and reduction in salt consumption (to less than 5 g, or 2,000 mg sodium per person per day) by 2025 would be about 20 cents per person per year in countries such as India and China, with the total package of priority interventions priced at about $9 billion per year, the authors said.

Keys to progress include leadership at the highest levels of government, a focus on prevention, treatment, international cooperation, monitoring, reporting and accountability, they said.

"An ideal outcome of the UN HLM will be a sustained commitment to a set of feasible actions and interventions for which specific and timed targets and indicators can be developed, and progress can be readily measured."

Dr. Beaglehole declared that he has no disclosures. Two of the authors declared financial relationships with pharmaceutical companies, and two others received grants from charities including the Wellcome Trust. One of the authors, Richard Horton, is editor of the Lancet. The others declared that they have no disclosures. ■

COMMENTARY

Dr. Stuart Garay, FCCP, comments: This affirms a mission dear to all physicians' hearts (especially those in the American College of Chest Physicians). While it is tremendous to propose this goal, it remains to be seen whether countries will devote the necessary resources to achieve it.

New Payment Models Debated

SGR • *from page 1*

The expert panel also stressed the importance of avoiding a "one size fits all" solution. "We should also have a realization that what will work in one part of the country will not work in another part of the country, and that's why we have continued to talk about a variety of options," said Dr. Cecil B. Wilson, president of the American Medical Association. "There is a temptation to feel like we ought to figure out one rule … that solves it all."

Dr. Wilson pointed to the provisions in the Affordable Care Act that allow for a variety of models of accountable care organizations, embodying the concept of options in the medical system. In that spirit, Dr. Wilson said that the AMA has formed a physician leadership group to evaluate the effectiveness of alternative payment methods.

Dr. David B. Hoyt, executive director of the American College of Surgeons, said the college is analyzing the use of bundled payments for surgery.

Dr. M. Todd Williamson, of the Coalition of State Medical and National Specialty Societies, introduced the option of private contracting, in which patients would be free to apply their benefits to a doctor of their choice, who would be free to opt out on a per-patient basis.

"Private contracting is a key principle of American freedom and liberty," Dr. Williamson said. "[It] will help the federal government achieve fiscal stability while fulfilling its promise to Medicare beneficiaries."

Harold Miller, executive director of the Center for Healthcare Quality and Payment Reform, suggested an episode-of-care payment plan through which hospitals and physicians jointly charge one price for all services included in a hospitalization. The model would also include a warranty stating that any infections or complications would be treated at no additional cost. A physician practice would receive one payment for all patient needs associated with chronic diseases or other conditions.

Rep. Burgess, who is also a doctor, said organizations should focus on ways to address patients with chronic conditions, adding that 80% of Medicare funding is spent by 20% of beneficiaries with chronic illnesses.

Courtesy American Medical Association

Panelists (from left to right) Dr. Mark B. McClellan, Dr. Cecil B. Wilson, Dr. David B. Hoyt, and Harold D. Miller presented SGR alternatives to Congress.

Is IPAB the New SGR?

Rep. Fred Upton (R-Mich.) raised concerns about the Independent Payment Advisory Board (IPAB), created by the Affordable Care Act. The board sets expenditure targets, on which it bases spending cuts. In 2018, targets will be based on the gross domestic product. "Sounds a lot like SGR, which we're trying to get rid of," Mr. Upton said. "Since hospitals are exempt from IPAB cuts through the rest of the decade, it seems that the IPAB has the potential to undermine any serious efforts at physician payment reform."

Some panelists agreed. "As presently constituted, we see it [as] basically another target for physicians to meet – potential double jeopardy, with an SGR as well as the pronouncements from this body," Dr. Wilson said.

The panelists also asserted their belief that whatever plan chosen should be physician led, with financial support of the government.

"It would be very helpful if physicians could get better financial support in their own payment system to enable them to lead all of those efforts," said Dr. Mark B. McClellan, director of the Engelberg Center for Healthcare Reform and former administrator of the Centers for Medicare and Medicaid Services. "Right now, with fee-for-service staying the way it is, they're staying behind." Dr. McClellan added that physicians can be the best sources for innovative and cost-saving mechanisms. ■

COMMENTARY

Dr. W. Michael Alberts, FCCP, comments: While probably well intentioned, the SGR legislation and formula have been widely criticized and, may I say, widely reviled since their passage. This article lists some of the proposals offered to replace the SGR. The key phrase, however, is in the first paragraph, namely, "could be unveiled." Perhaps we should not hold our collective breath.

Medication Reconciliation Requirements Debut July 1

BY MARY ELLEN SCHNEIDER
Elsevier Global Medical News

Starting in July, hospitals, nursing homes, office-based surgical practices, and other health care organizations accredited by the Joint Commission will need to comply with new requirements for medication reconciliation.

Officials at the Joint Commission have approved a revised national patient safety goal on medication reconciliation that requires providers at accredited organizations to find out what medications patients are taking when they are admitted to the hospital or arrive at the facility, and compare that information with any new medications ordered. Providers must also give the patient or family a list of the medications that should be taken once they leave the facility.

PROVIDERS MUST GIVE THE PATIENT OR FAMILY A LIST OF THE MEDICATIONS THAT SHOULD BE TAKEN ONCE THEY LEAVE THE FACILITY.

The Joint Commission is also asking providers to do something new: Educate patients and their families about the importance of maintaining a list of current medications. For example, hospital staff could fulfill this goal by advising patients to give the reconciled medication lists to their primary care physicians.

The Joint Commission's requirements differ somewhat depending on the setting of care. For example, in settings where medications are not prescribed, providers will not be required to compare old and new medications, or to give patients written information on the medications they should be taking. They will also not be required to provide education on medication management.

These new requirements replace a national patient safety goal on medication reconciliation from 2009, which was placed on hold due to concerns from physicians and hospitals that it was too prescriptive. Since then, officials at the Joint Commission have been talking to physicians and other providers about their concerns, and working to revise the requirements.

"We really tried to work with the field to find out what the goal should be all about," Maureen Carr, project director for the division of health care quality evaluation at the Joint Commission, said in an interview.

Ms. Carr said the previous medication reconciliation goal was much more prescriptive and included requirements related to several elements of the care process that were already addressed in other Joint Commission goals. This time around, officials tried to simplify the requirements by focusing on "risk points" associated with medication reconciliation. They also tried to minimize the documentation requirements.

And they backed away from some of the more prescriptive elements, Ms. Carr said. For example, the goal used to require that providers give the reconciled medication list to the next provider of care. But that was problematic because in some situations there wasn't a next provider of care, she said. Now the requirement is to give the list to the patient or family.

The revised goal also spells out that making a "good faith effort" to get an accurate medication list would meet the intent of the standard. Officials at the Joint Commission understand that it's difficult to get a correct medication list from patients for a number of reasons, ranging from patients who withhold information to those that simply forget, Ms. Carr said. It has been the position of the Joint Commission that a good faith effort is enough, but they decided to make that explicit in the policy, she said.

While the burden on providers should be lessened under the revised goal, Ms. Carr said it still addresses patient safety by targeting the most critical areas. For example, the new requirements focus on getting information from the patients when they come in, comparing current medications with new ones, and ensuring that patients understand their medications when the episode of care is over. ■

Shorter Combo Therapy Effective for Latent TB

BY SUSAN LONDON
Elsevier Global Medical News

DENVER – Shorter combination therapy was at least as efficacious as conventional longer monotherapy for preventing tuberculosis in patients with latent infection, according to final results of the PREVENT TB trial.

The phase III trial, also known as TB Trials Consortium Study 26, was conducted in patients with latent TB infection at high risk for progression.

After 33 months, the cumulative rate of TB disease was 0.19% in the group given 3 months of weekly rifapentine (RIF) plus isoniazid (INH) under direct observation (3HP), compared with 0.43% in the group given 9 months of self-administered daily INH. The difference between groups was well within the trial's boundary set for noninferiority, lead investigator Dr. Timothy R. Sterling reported at an international conference of the American Thoracic Society.

Despite more adverse events leading to withdrawal from treatment, patients given the shorter combination therapy were still more likely to complete treatment.

The trial's findings suggest that "3HP is an alternative to 9H for treatment of latent [TB] infection in persons at high risk for progression to tuberculosis," he said.

"3HP was as effective as 9H, but in operational settings 3HP could be more effective than 9H, particularly if 3HP is given under direct observation and 9H has completion rates of approximately 30%-60%," Dr. Sterling noted.

The trial enrolled 8,053 patients older than 2 years from the United States, Canada, Brazil, and Spain who had a positive tuberculin skin test (or in the case of young children, close contact with someone with TB), plus risk factors for progression.

The patients were randomly assigned in nearly equal numbers and treated on an open-label basis. The 3HP group was given once-weekly RIF (Priftin) 900 mg, plus INH (Nydrazid) 15-25 mg/kg, by directly observed treatment for 3 months. The 9H group was given daily self-administered INH 5-15 mg/kg for 9 months.

All patients also received vitamin B_6. They were followed for 33 months from enrollment. The patients had a median age of 37 years, 58% were white, and 3% were HIV positive, reported Dr. Sterling, a professor of medicine and director of epidemiology research in the division of infectious diseases at the Vanderbilt Institute for Global Health in Nashville, Tenn.

In modified intention-to-treat analyses, the cumulative rate of culture-confirmed TB was 0.19% in the 3HP group, compared with 0.43% in the 9H group. The upper bound of the 95% confidence interval for the difference between these rates was 0.01% – far below the trial's predefined noninferiority margin of 0.75%.

In per-protocol analyses, the cumulative rates were 0.13% and 0.32%, respectively. The upper bound of the 95% confidence interval for the difference between these rates was 0.06%, well below the noninferiority margin.

Compared with the 9H regimen, 3HP was associated with a higher treatment completion rate (82% vs. 69%) and a lower rate of hepatotoxicity (0.5% vs. 2.7%).

The 3HP regimen was also associated with higher rates of any adverse event attributable to the drug(s) (8.1% vs. 5.5%) and of permanent drug discontinuation because of adverse events (4.7% vs. 3.6%). Neither rates of grade 3 and 4 toxicity nor rates of death differed significantly between groups.

The Centers for Disease Control and Prevention and the American Thoracic Society will be updating their TB recommendations when the data are published, according to Dr. Sterling.

"Uptake of the 3HP regimen will depend on availability of rifapentine, but the manufacturer, Sanofi-Aventis, is committed to this," Dr. Sterling added.

It will be important for TB treatment programs to be able to monitor for adverse events, Dr. Sterling cautioned, given that previous experience suggests some TB regimens have poorer tolerability in the general population than in a clinical trial.

The shorter, more potent TB treatment regimen might improve patient adherence, said Dr. Kenneth Castro, director of the division of TB elimination at the Centers for Disease Control and Prevention. Practitioners are always struggling to get patients to complete a 9-month regimen for TB, but with limited success, he said. ■

VITALS

Major Finding: Compared with their counterparts given longer therapy with isoniazid, patients given shorter therapy with rifapentine plus isoniazid were less likely to develop culture-confirmed tuberculosis (0.19% vs. 0.43%).

Data Source: A randomized, open-label, noninferiority phase III trial among 8,053 individuals with latent tuberculosis infection who were at high risk for progression to tuberculosis disease.

Disclosures: Dr. Sterling and Dr. Castro reported having no relevant conflicts of interest. Sanofi-Aventis provided rifapentine for the trial.

Human Lung Stem Cells Discovered

BY MARY ANN MOON
Elsevier Global Medical News

Researchers believe that they have isolated human lung stem cells for the first time.

Cells from normal human lung tissue obtained from 12 unused donor lungs were identified as stem cells using the stem-cell antigen c-kit. These lung cells were then expanded and, in a series of in vitro and in vivo studies, the researchers demonstrated the three properties fundamental to stem cells: self-renewal, clonogenicity, and multipotentiality, said Jan Kajstura, Ph.D., of the departments of anesthesia and medicine at Brigham and Women's Hospital and Harvard Medical School, Boston, and associates.

The undifferentiated cells were nested in niches within the distal airways in the lung samples. Other types of stem cells also typically are located in such anatomical niches, the researchers noted.

In addition to these cells from adult donor lungs, identical cells also were found in lung tissue specimens from nine cases of fetal death.

When the stem cells were transplanted into deliberately injured mouse lungs, they became structurally and functionally integrated into the damaged organs and created human bronchioles, alveoli, and pulmonary vessels within 14 days, Dr. Kajstura and colleagues said (N. Engl. J. Med. 2011;364:1795-806).

These findings indicate that the lung stem cells might play a crucial role in lung tissue regeneration after injury and in lung tissue homeostasis, they said.

This study was supported by the National Institutes of Health and Cardiocentro Ticino. A patent has been filed for this class of human lung stem cells on behalf of Partners HealthCare (which includes Brigham and Women's Hospital). Dr. Kajstura reported no conflicts; a coauthor reported ties to Autologous. ■

COMMENTARY

Dr. Joseph B. Barney, FCCP, comments: Lung stem cells with the ability to propagate and differentiate on the appropriate extracellular matrix are very exciting. The hope of engraftment in patients with advanced lung disease is certainly closer at hand given this discovery. Whether these undifferentiated cells will express donor HLA surface antigens or not will be vital in determining long-term rejection in recipients.

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CDC: Asthma Rates Continue to Rise

BY DIANA MAHONEY
Elsevier Global Medical News

VITALS

Major Finding: The prevalence of asthma among people of all ages in the United States increased from 20.3 million (7.3%) in 2001 to 24.6 million (8.2%) in 2009.

Data Source: Data from the 2001-2009 National Health Interview Survey and the 2001, 2005, and 2009 state-based Behavioral Risk Factor Surveillance System.

Disclosures: Dr. Arias and Dr. Garbe disclosed no financial conflicts of interest.

Despite national efforts to improve the quality of care and health outcomes of individuals with asthma, the overall prevalence of the chronic respiratory disease in the United States increased by more than 12% between 2001 and 2009, according to a report released by the Centers for Disease Control and Prevention.

Based on data from the 2001-2009 National Health Interview Survey and the 2001, 2005, and 2009 state-based Behavioral Risk Factor Surveillance System, the prevalence of asthma among people of all ages increased from 20.3 million (7.3%) in 2001 to 24.6 million (8.2%) in 2009, the agency reported. The prevalence among children younger than 18 years increased from 8.7% to 9.6% during this period, with the highest prevalence rates observed among poor children (13.5%), non-Hispanic black children (17.0%), and boys (11.3%). Among adults, asthma prevalence increased from 6.9% in 2001 to 7.7% in 2009, with the highest rates seen in poor adults (10.6%) and in women (9.7%), according to the report (MMWR 2011;60:1-7).

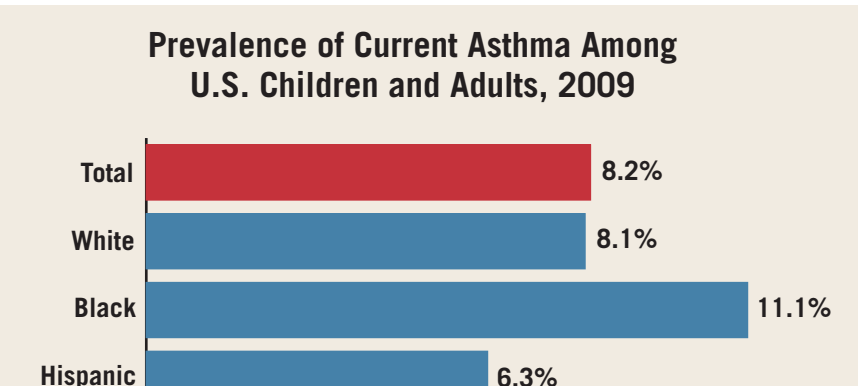
"Approximately 1 out of every 12 individuals in the United States has asthma, and the number is rising," said Ileana Arias, Ph.D., principal deputy director of the CDC. "The estimated total cost of asthma in terms of medical expenses, lost school or work days, and premature death was $56 billion in 2007," she said in a press briefing.

A review of the data for 2008 showed that "more than half [52.6%] of the people with asthma reported having an attack within the prior year. Nearly 42% missed 1 or more days of work or school because of their asthma, 26% visited the emergency department or urgent care center for treatment, and 7% were hospitalized," Paul Garbe, DVM, chief of the CDC's Air Pollution and Respiratory Health Branch, said during the press briefing. "The estimated per person/per year medical expenses associated with asthma between 2002 and 2007 was $3,259."

Assessing gaps in health care coverage and access could alter the asthma landscape, Dr. Garbe said. "Of the nearly 90% of asthma patients with health insurance, approximately 12% reported not being able to afford their prescription medicine, 37% had ever seen or talked to a specialist physician about their asthma, and 86% had ever talked to a primary care provider about it," he said. Among the uninsured asthma population, 40% reportedly couldn't afford medication, nearly 20% had seen or talked to an asthma specialist, and 60% had seen or talked to a primary care physician about their asthma.

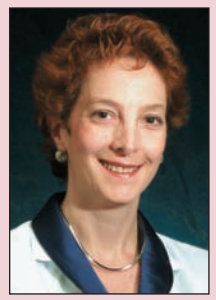
Further, although it is well understood that optimal asthma control includes self-management training, appropriate use of inhaled corticosteroids, and avoidance of environmental allergens and irritants, only one-third of the population had ever been given an action plan as recommended by the National Institute of Health's National Asthma Education and Prevention Program (NAEPP), Dr. Garbe said. An NAEPP action plan addresses the asthma-related needs and circumstances of individual patients.

Although potentially limited by the fact that the databases used are based on self-report and thus are vulnerable to recall bias, the findings suggest that people with asthma are doing a suboptimal job of managing their symptoms and that coordinated efforts at the local, state, and national levels should target patient education. Evidence-based interventions to reduce environmental risk factors for asthma also are needed, Dr. Garbe said. ■



COMMENTARY

Dr. Jeana O'Brien, FCCP, comments: As noted in the comments by Dr. Arias and Dr. Garbe, national surveys show a small but significant increase in the prevalence of asthma. The economic and care implications of even small increases in this common lung disease are quite significant given the numbers of patients affected. It is somewhat discouraging to note the low incidence of specialty involvement with these patients, given other literature showing the beneficial impact of specialty involvement. Team-based care with high levels of patient engagement are likely to have the greatest impact – along with ensuring access to medication – in lessening morbidity and mortality from asthma. Perhaps this will occur with increasing attention to medical home models of care and continued efforts at reducing environmental risk factors.



Genetic Link Found to IPF, Interstitial Pneumonia

BY MARY ANN MOON
Elsevier Global Medical News

A genetic variant in the MUC5B gene appears to be associated with both idiopathic pulmonary fibrosis and familial interstitial pneumonia.

The MUC5B gene encodes mucin 5B, a gel-forming protein that is usually found in the lungs and is overexpressed in pulmonary diseases such as asthma, bronchitis, COPD, and cystic fibrosis. "Our findings suggest that dysregulated MUC5B expression in the lung may be involved in the pathogenesis of pulmonary fibrosis," said Max A. Seibold, Ph.D., of National Jewish Health, Denver, and his associates.

In addition, the link with familial interstitial pneumonia "could provide insight into the particular clinical manifestations of this complex disease process and consequently lead to earlier detection, more predictable prognosis, and personalized therapeutic strategies," they said.

Until now, the genetic mutations that have been implicated in both idiopathic pulmonary fibrosis (IPF) and familial interstitial pneumonia (FIP) have accounted for only a small proportion of the population risk for the disorders. The investigators searched further for other related mutations, beginning with a genomewide linkage scan in 82 families with FIP.

The results led the researchers to assess genetic variation in particular regions of three gel-forming mucin genes, using blood samples from a separate cohort of 83 subjects who had FIP, 492 subjects who had IPF, and 322 controls. One single-nucleotide polymorphism in the putative promoter of the MUC5B gene was particularly strongly associated with both disorders. The minor allele of this SNP (rs35705950) was found at a frequency of 34% among subjects with FIP and 38% among those with IPF, compared with only 9% among controls.

A subsequent analysis showed that rs35705950 exerted an effect in both disorders that was strongly independent of that of other, known mucin variants.

Next, the investigators evaluated the effect of rs35705950 on MUC5B expression in lung tissue from 33 subjects with IPF and 47 control subjects. They found that MUC5B expression was 14 times higher in samples from affected patients than in those from control subjects.

COMMENTARY

Dr. Joseph B. Barney, FCCP, comments: I think this area of research is fundamentally important in the global understanding of IPF as we have been focusing for years on inflammatory processes and fibrogenic areas in lung parenchyma and not looking much at the role of distal airways may play in the development of dysregulated fibrosis. The prospect of a new model of pulmonary fibrosis with significant interactions between mucins and the interstitium is thinking outside the box whose time has come.

Finally, immunohistochemical staining of the lung tissue from IPF patients showed regions of dense accumulation of MUC5B in areas of microscopic honeycombing that are characteristic of IPF lesions. There was patchy staining of the metaplastic epithelia lining the honeycomb cysts, and of the mucus plugs within the cysts, the investigators said (N. Engl. J. Med. 2011;364:1503-12).

This study was supported by the National Institute of Environmental Health Sciences, the National Cancer Institute, the American Lung Association, the Cystic Fibrosis Foundation, the Chapman Foundation, InterMune, and the National Heart, Lung, and Blood Institute. Dr. Seibold's associates reported ties to numerous academic, government, and industry sources. ■

Rivaroxaban Edges Out Enoxaparin in VTE Prevention

BY PATRICE WENDLING
Elsevier Global Medical News

NEW ORLEANS – The investigational oral anticoagulant rivaroxaban was as effective as injection enoxaparin in preventing venous thromboembolism at 10 days and superior at 35 days among critically ill hospitalized patients in the phase III MAGELLAN study.

Overall bleeding rates were low, at about 1%, but were significantly higher in patients receiving rivaroxaban across the entire study period, Dr. Alexander T. Cohen said at the annual meeting of the American College of Cardiology.

"MAGELLAN confirms that there is a continued risk of VTE beyond the initial period of hospitalization, and I believe this is an important finding because the benchmark data said we should get a figure of 4%, and we got a figure of 5.7% at day 45," he said.

The study randomly assigned 8,101 patients hospitalized for an acute medical illness including heart failure, acute infectious disease, and acute respiratory insufficiency to oral rivaroxaban 10 mg daily for 35 days or subcutaneous enoxaparin 40 mg daily for 10 days plus placebo.

At day 10, the primary composite efficacy end point, defined as the cumulative incidence of asymptomatic proximal deep vein thrombosis detected by ultrasonography, symptomatic DVT, symptomatic nonfatal pulmonary embolism, and VTE-related death, occurred in 2.7% of patients in both arms, reaching the prespecified noninferiority benchmark for day 10.

At 35 days, significantly fewer rivaroxaban patients experienced the primary efficacy end point, at 4.4% vs. 5.7% of patients in the enoxaparin arm reaching the superiority end point for day 35. The absolute risk reduction was 1.3% and the relative risk reduction was 23%, said Dr. Cohen, of King's College in London.

Clinically relevant bleeding occurred significantly more often in the rivaroxaban group than in the enoxaparin group from day 1 to 10 (2.8% vs. 1.2%), from day 1 to 35 (4.1% vs. 1.7%), and from day 11 to 35 (1.4% vs. 0.5%).

Among major bleeding events, a drop in hemoglobin of 2 g/dL or more was observed in 31 rivaroxaban patients and 10 enoxaparin patients; 2 or more units of blood were transfused in 34 and 8 patients, respectively; and critical site bleeds occurred in 9 and 4 patients, respectively.

Notably, seven rivaroxaban patients died of fatal bleeds, compared with only one enoxaparin patient. Overall, about 5% of patients in the trial died of all causes.

The net clinical benefit was 9.4% for rivaroxaban and 7.8% for enoxaparin. Based on the prespecified net clinical benefit analysis, Dr. Cohen acknowledged that a consistently positive benefit-risk balance was not seen among the cohort, but said they plan to conduct subgroup analyses to determine factors related to bleeding and to identify patients who might derive greater benefit from thromboprophylaxis with rivaroxaban.

He stressed that the study used a highly sensitive analysis of bleeding such as a drop in hemoglobin of just 2 g/dL, and that even nosebleeds and bruising were counted in the risk-benefit analysis. When asked whether removal of these lesser bleeding events would result in a positive clinical benefit for rivaroxaban, Dr. Cohen said he was hesitant to speculate outside the trial's prespecified outcome measures. When pressed further, he replied, "If we looked at a traditional risk-benefit analysis of major bleeds, then the picture swings back the other way. ... It would start to look more favorable toward rivaroxaban, but I have to stick to the study protocol."

When asked whether he had a theory as to why fatal bleeds occurred, Dr. Cohen pointed out that while there were 7 bleeding deaths with rivaroxaban and only 1 with enoxaparin, there were 30 PE-related deaths with enoxaparin and 19 with rivaroxaban. "So we saved 11 lives from blood clots, if you want to [make that sort of analysis], and lost 6 lives through bleeding," he said.

In a separate interview, Dr. A. Michael Lincoff, director of the Cleveland Clinic Coordinating Center for Clinical Research, said many studies have shown that the risk of DVT persists after acute hospitalization, and the ability to give rivaroxaban after patients are discharged is valuable. "It's a much more practical drug to send patients home on," he said.

Dr. Cohen reported financial ties with more than a dozen pharmaceutical companies, including Bayer (maker of rivaroxaban). Dr. Lincoff had no relevant disclosures. ■

COMMENTARY

Dr. Jun Chiong, FCCP, comments: Being able to replace injectable anticoagulant for DVT prophylaxis is a huge accomplishment. The success of the MAGELLAN study means that injectable heparin will eventually become redundant. The efficacy of rivaroxiban for acute PE therapy is a more important question that is much harder to answer, and at the moment is based more on opinion than fact.

Statement Addresses Severe Manifestations of VTE

BY MIRIAM E. TUCKER
Elsevier Global Medical News

A recently released scientific statement from the American Heart Association provides guidance for the management of the more severe forms of venous thromboembolism.

The statement focuses on three areas: massive and submassive pulmonary embolism (PE), iliofemoral deep vein thrombosis (DVT), and chronic thromboembolic pulmonary hypertension. "The goal is to provide practical advice to enable the busy clinician to optimize the management of patients with these severe manifestations of VTE," said the writing committee, cochaired by Dr. Michael R. Jaff and Dr. M. Sean McMurtry (Circulation 2011;123:1788-830).

In an interview, Dr. McMurtry noted that because these disease areas have less data to support management strategies than do other areas of cardiovascular medicine, most of the recommendations in the document are class II ("it is reasonable" or "may be considered") with level of evidence B or C (limited populations evaluated). "The authors hope that this document will inspire more research into these conditions," said Dr. McMurtry of the University of Alberta, Edmonton.

Massive and Submassive PE

The document begins by defining "massive," "submassive," and "low-risk" PE, and provides data for the various techniques, including clinical scores, echocardiography, CT, elevated troponins/natriuretic peptides, and electrocardiography, that can be used to identify patients at increased risk for adverse short-term outcomes in acute PE.

Beyond initial heparin anticoagulation therapy, the use of fibrinolytic drugs is reasonable for patients with massive acute PE and an acceptable risk of bleeding complications, the statement said. It may also be considered for patients with submassive acute PE judged to have clinical evidence of an adverse prognosis (new hemodynamic instability, worsening respiratory insufficiency, severe right ventricle [RV] dysfunction, or major myocardial necrosis) and a low risk of bleeding complications.

Fibrinolysis is not recommended for patients with low-risk PE, or submassive PE with minor RV dysfunction, minor myocardial necrosis, and no clinical worsening. Fibrinolysis is also not recommended for undifferentiated cardiac arrest, wrote Dr. McMurtry, Dr. Jaff of Harvard Medical School, Boston, and their coauthors.

In addition, recommendations are provided for other areas in which data are sparse and optimal management is unclear, including catheter-based therapies. Transcatheter procedures can be performed as an alternative to thrombolysis when there are contraindications or when emergency surgical thrombectomy is unavailable or contraindicated. Catheter interventions can also be performed when thrombolysis has failed to improve hemodynamics in the acute setting.

Hybrid therapy that includes both catheter-based clot fragmentation and local thrombolysis is an emerging strategy, the committee noted.

Adult patients with any confirmed acute PE who have contraindications to anticoagulation or have active bleeding should receive an inferior vena cava (IVC) filter. Further specific guidance is given for the type of filter and for monitoring.

Iliofemoral Deep Vein Thrombosis

IFDVT refers to complete or partial thrombosis of any part of the iliac vein or the common femoral vein, with or without involvement of other lower-extremity veins or the IVC. Under this heading, the document addresses the use of initial coagulant therapy, long-term anticoagulant therapy, compression therapy, IVC filters, and thromboreductive strategies, including systemic, catheter-directed, percutaneous mechanical, and pharmacomechanical thrombolysis. Surgical venous thrombectomy is also discussed as an alternative method of thrombus removal in IFDVT.

"Reasonable" angiopathy and stenting options for older adolescents and adults include the use of percutaneous transluminal venous angioplasty and stent placement in the iliac vein to treat obstructive lesions after catheter-directed thrombolysis (CDT), pharmacomechanical CDT (PCDT), or surgical venous thrombectomy, and placement of iliac vein stents to reduce postthrombotic symptoms and heal venous ulcers in patients with advanced postthrombotic symptoms and iliac vein obstruction. "For obstructive iliac vein lesions that extend into the common femoral vein, caudal extension of stents into the common femoral vein is reasonable if unavoidable," they wrote. Guidelines regarding subsequent therapeutic anticoagulation are also provided.

Chronic Thromboembolic Pulmonary Hypertension

The section on CTEPH outlines the incidence, pathophysiology, classification, risk factors, natural history, clinical presentation, diagnosis, and treatment with pulmonary endarterectomy and medical therapies. The condition is a syndrome of dyspnea, fatigue, and exercise intolerance caused by proximal thromboembolic obstruction and distal remodeling of the pulmonary circulation that leads to elevated pulmonary artery pressure and progressive RV failure, the statement said.

Patients presenting with unexplained dyspnea, exercise intolerance, or clinical evidence of right-sided heart failure, with or without a prior history of symptomatic venous thromboembolism, should be evaluated for CTEPH, and it is reasonable to evaluate patients with an echocardiogram 6 weeks after an acute pulmonary embolism to screen for persistent pulmonary hypertension that may predict the development of CTEPH.

Patients with objectively proven CTEPH should be promptly evaluated for pulmonary endarterectomy, even if symptoms are mild, and receive indefinite therapeutic anticoagulation in the absence of contraindications, they advised.

In the interview, Dr. McMurtry said that other guidelines address various aspects of VTE, including the American College of Chest Physicians guidelines on VTE prevention (Chest 2008;133:381S-453S) and the European Society of Cardiology guidelines for PE management (Eur. Heart J. 2008;29:2276-315). "What is different about this statement is that it has a narrow focus on extreme forms of venous thromboembolism to help the clinician decide whether more aggressive therapies beyond anticoagulation are indicated. This focus and level of detail [are] not found in other documents."

Dr. McMurtry stated that he has no relevant financial disclosures. Dr. Jaff disclosed that he has served as a speaker for, or an adviser to, Bacchus Vascular, Abbott Vascular, Boston Scientific, Covidien, and Medtronic Vascular. Several coauthors reported having research grant, speakers bureau, or advisory ties to other pharmaceutical or device companies. The AHA received no financial support for the development of the statement. ■

COMMENTARY

Dr. Jun Chiong, FCCP, comments: Admittedly in clinical practice, the widespread use of echocardiography has led to the discovery of pulmonary hypertension and RV dysfunction. With the AHA integrated guidelines, the decision regarding thrombolysis, embolectomy, or angioplasty becomes much easier, especially for the cardiologist reading the echocardiogram.

Even Short-Term NSAID Use Raises Risk in Heart Patients

BY ELIZABETH MECHCATIE
Elsevier Global Medical News

For patients with a history of myocardial infarction, any length of treatment with nonsteroidal anti-inflammatory drugs poses an unacceptably high risk for death or recurrent heart attack, based on findings from a Danish study using hospital and pharmacy registry data.

"Even short-term NSAID treatment is associated with increased cardiovascular risk in patients with prior MI," the authors stressed. The significant risk elevation began during the first week of therapy and continued through the course of treatment, with some differences in the magnitude of risk between NSAIDs.

"These results challenge the view that NSAIDs are not harmful during short-term treatment and indicate that a revision of current recommendations regarding NSAID treatment in patients with established cardiovascular disease is required," said Anne-Marie Schjerning, department of cardiology, Copenhagen University Hospital (Denmark), and coauthors (Circulation 2011;123:2226-35).

Of the 83,675 people aged 30 years and older who had had their first MI in 1997-2006 identified in the national registries (mean age, 68 years), 42% had received NSAIDs. Treatment with NSAIDs was linked with a 45% greater risk of death/recurrent MI during the first 7 days of treatment, which persisted and increased by 65% over a 30- to 90-day period of treatment.

COMMENTARY

Dr. Jun Chiong, FCCP, comments: As in previous studies, an increased risk of cardiovascular and cerebrovascular events was seen with NSAIDs. However, NSAID exposure was associated with a reduced risk of death in some studies. This study raises important questions about long-term NSAID use by patients with osteoarthritis, as well as questions about publication bias. In any case, NSAID use should be as short term as possible, and a large-scale prospective study is needed.

The greatest risk identified was with diclofenac (hazard ratio, 3.26; 95% confidence interval, 2.57-3.86 for death/MI at day 1-7 of treatment). Diclofenac is available over the counter in many countries.

A significant increase in risk was seen after 1 week of treatment with ibuprofen, in the first week of treatment with rofecoxib (which has been withdrawn from the market), and after 14-30 days with celecoxib. The risk associated with ibuprofen was lower than the risk associated with the two COX-2 selective inhibitors, rofecoxib and celecoxib, and with diclofenac. There was no increased risk of death or recurrent MI associated with naproxen; however, in one study, naproxen was associated with an increased risk of GI bleeding, compared with rofecoxib, the authors noted.

Despite study limitations such as observational design and possible information bias, the investigators added: "The accumulating evidence suggests that we must limit NSAID use to the absolute minimum in patients with established cardiovascular disease."

The authors had no relevant financial disclosures. ■

Important safety information

Because of the risks of liver injury and birth defects, Tracleer may be prescribed and dispensed only through the Tracleer Access Program (T.A.P.), a restricted distribution program, by calling 1-866-228-3546. Only prescribers and pharmacies registered with T.A.P. may prescribe and distribute Tracleer. Tracleer may be dispensed only to patients who are enrolled in and meet all conditions of T.A.P.

Liver injury

Elevations of liver aminotransferases (ALT, AST) and liver failure have been reported with Tracleer. In a setting of close monitoring, rare cases of liver failure and unexplained hepatic cirrhosis were observed after prolonged treatment. In general, avoid using Tracleer in patients with elevated aminotransferases (>3 × ULN). Measure liver aminotransferases prior to initiation of treatment and then monthly. Discontinue Tracleer if aminotransferase elevations are accompanied by signs or symptoms of liver dysfunction or injury or increases in bilirubin ≥2 × ULN.

Teratogenicity

Based on animal data, Tracleer is likely to cause major birth defects if used during pregnancy. Exclude pregnancy before and during treatment. To prevent pregnancy, females of childbearing potential must use 2 reliable forms of contraception during treatment and for 1 month after stopping Tracleer unless the patient has a tubal sterilization or Copper T 380A IUD or LNg-20 IUS inserted, in which case no other contraception is needed. Monthly pregnancy tests should be obtained.

Contraindications

Tracleer is contraindicated with cyclosporine A, glyburide, in females who are or may become pregnant, or in patients who are hypersensitive to bosentan or any component of Tracleer.

Warnings and precautions

In clinical trials, Tracleer caused ALT/AST elevations (>3 × ULN) in 11% of patients accompanied by elevated bilirubin in a few cases. The combination of hepatocellular injury (increases in aminotransferases of >3 × ULN) and increases in total bilirubin (≥3 × ULN) is a marker for potential serious liver injury. Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. Avoid using Tracleer in patients with moderate or severe liver impairment or elevated ALT/AST >3 × ULN.

If clinically significant fluid retention develops, with or without associated weight gain, the cause, such as Tracleer or underlying heart failure, must be determined. Patients may require treatment or Tracleer therapy may need to be discontinued.

Preclinical data and an open-label safety study (N=25) showed a decline in sperm count of ≥50% in 25% of Tracleer-treated patients after 3 or 6 months. After 6 months, sperm count remained in normal range, with no changes in sperm morphology or motility, or hormone levels. Endothelin receptor antagonists such as Tracleer may adversely affect spermatogenesis.

Treatment with Tracleer can cause a dose-related decrease in hemoglobin (Hgb) and hematocrit. Hgb should be checked after 1 and 3 months, and then every 3 months. Upon marked decrease in Hgb, determine the cause and need for specific treatment.

If signs of pulmonary edema occur, the possibility of associated pulmonary veno-occlusive disease should be considered. Tracleer should be discontinued.

Adverse events

In Tracleer pivotal trials, the most common adverse events occurring more often in Tracleer-treated patients than in patients taking placebo (≥2%) were respiratory tract infection, edema, hypotension, sinusitis, arthralgia, liver function test abnormal, palpitations, and anemia.

CELEBRATING 10 YEARS OF PUTTING PATIENTS FIRST

Introducing the Tracleer Patient Coupon Program—patients pay no more than $10 per month for Tracleer.

NOVEMBER '11

Since bringing the first ERA to market 10 years ago, we have been continually inspired by patients and the dedication of the medical community.

Ten years and 82,000 patients later, we at Actelion are celebrating this decade of commitment by helping to ensure that patients pay no more than $10 monthly for therapy. Actelion will contribute up to $10,000 annually per patient.*

Indication

Tracleer is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital systemic-to-pulmonary shunts (18%). Patients with WHO class II symptoms showed reduction in the rate of clinical deterioration and a trend for improvement in walk distance. Physicians should consider whether these benefits are sufficient to offset the risk of liver injury in WHO class II patients, which may preclude future use as their disease progresses.

Please see accompanying brief summary of prescribing information, including ***BOXED WARNING*** *about liver injury and pregnancy, on following pages.*

*Patients ineligible for the Tracleer Patient Coupon Program include any patients whose prescriptions are paid for by the government, Medicare, Medicaid, VA/DOD (Tricare), or Indian Health Service, patients in Massachusetts and Puerto Rico, or where prohibited by law.

ACTELION

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Tracleer® BOSENTAN TABLETS

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Trim Line

WARNING: RISKS OF LIVER INJURY and TERATOGENICITY

Because of the risk of liver injury and birth defects, Tracleer is available only through a special restricted distribution program called the Tracleer Access Program (T.A.P.), by calling 1 866 228 3546. Only prescribers and pharmacies registered with T.A.P. may prescribe and distribute Tracleer. In addition, Tracleer may be dispensed only to patients who are enrolled in and meet all conditions of T.A.P. [see **Warnings and Precautions**].

Liver Injury

In clinical studies, Tracleer caused at least 3-fold upper limit of normal (ULN) elevation of liver aminotransferases (ALT and AST) in about 11% of patients, accompanied by elevated bilirubin in a small number of cases. Because these changes are a marker for potential serious liver injury, serum aminotransferase levels must be measured prior to initiation of treatment and then monthly [see **Dosage and Administration, Warnings and Precautions**]. In the postmarketing period, in the setting of close monitoring, rare cases of unexplained hepatic cirrhosis were reported after prolonged (> 12 months) therapy with Tracleer in patients with multiple co-morbidities and drug therapies. There have also been reports of liver failure. The contribution of Tracleer in these cases could not be excluded.

In at least one case, the initial presentation (after > 20 months of treatment) included pronounced elevations in aminotransferases and bilirubin levels accompanied by non-specific symptoms, all of which resolved slowly over time after discontinuation of Tracleer. This case reinforces the importance of strict adherence to the monthly monitoring schedule for the duration of treatment and the treatment algorithm, which includes stopping Tracleer with a rise of aminotransferases accompanied by signs or symptoms of liver dysfunction [see **Dosage and Administration**].

Elevations in aminotransferases require close attention [see **Dosage and Administration**]. Tracleer should generally be avoided in patients with elevated aminotransferases (> 3 x ULN) at baseline because monitoring liver injury may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥ 2 x ULN, treatment with Tracleer should be stopped. There is no experience with the re-introduction of Tracleer in these circumstances.

Teratogenicity

Tracleer is likely to cause major birth defects if used by pregnant females based on animal data [see **Contraindications**]. Therefore, pregnancy must be excluded before the start of treatment with Tracleer. Throughout treatment and for one month after stopping Tracleer, females of childbearing potential must use two reliable methods of contraception unless the patient has a tubal sterilization or Copper T 380A IUD or LNg 20 IUS inserted, in which case no other contraception is needed. Hormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives should not be used as the sole means of contraception because these may not be effective in patients receiving Tracleer [see **Drug Interactions**]. Monthly pregnancy tests should be obtained.

INDICATIONS AND USAGE

Pulmonary Arterial Hypertension

Tracleer® is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominately patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital systemic-to-pulmonary shunts (18%).

Considerations for use

Patients with WHO Class II symptoms showed reduction in the rate of clinical deterioration and a trend for improvement in walk distance. Physicians should consider whether these benefits are sufficient to offset the risk of liver injury in WHO Class II patients, which may preclude future use as their disease progresses.

DOSAGE AND ADMINISTRATION

Recommended Dosing

Tracleer treatment should be initiated at a dose of 62.5 mg twice daily for 4 weeks and then increased to the maintenance dose of 125 mg twice daily. Doses above 125 mg twice daily did not appear to confer additional benefit sufficient to offset the increased risk of liver injury.

Tablets should be administered morning and evening with or without food.

Required Monitoring

Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated.

Dosage Adjustments for Patients Developing Aminotransferase Elevations

The table below summarizes the dosage adjustment and monitoring recommendations for patients who develop aminotransferase elevations >3 X ULN during therapy with Tracleer. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥ 2 x ULN, treatment with Tracleer should be stopped. There is no experience with the re-introduction of Tracleer in these circumstances.

Table 1: Dosage Adjustment and Monitoring in Patients Developing Aminotransferase Elevations >3 x ULN

ALT/AST levels	Treatment and monitoring recommendations
> 3 and ≤ 5 x ULN	Confirm by another aminotransferase test; if confirmed, reduce the daily dose to 62.5 mg twice daily or interrupt treatment, and monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pre-treatment values, continue or re-introduce the treatment as appropriate (see below).
> 5 and ≤ 8 x ULN	Confirm by another aminotransferase test; if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks. Once the aminotransferase levels return to pre-treatment values, consider re-introduction of the treatment (see below).
> 8 x ULN	Treatment should be stopped and re-introduction of Tracleer should not be considered. There is no experience with re-introduction of Tracleer in these circumstances.

If Tracleer is re-introduced it should be at the starting dose; aminotransferase levels should be checked within 3 days and thereafter according to the recommendations above.

Use in Females of Childbearing Potential

Initiate treatment in females of child-bearing potential only after a negative pregnancy test and only in females who are using two reliable methods of contraception. Females who have had a tubal sterilization or a Copper T 380A IUD or LNg 20 IUS inserted do not require other forms of contraception. Effective contraception must be practiced throughout treatment and for one month after stopping Tracleer. Females should seek contraceptive advice as needed from a gynecologist or similar expert. Urine or serum pregnancy tests should be obtained monthly in females of childbearing potential taking Tracleer [see **Boxed Warning, Contraindications, Drug Interactions**].

Use in Patients with Pre-existing Hepatic Impairment

Tracleer should generally be avoided in patients with moderate or severe liver impairment. There are no specific data to guide dosing in hepatically impaired patients; caution should be exercised in patients with mildly impaired liver function [see **Warnings and Precautions**].

Patients with Low Body Weight

In patients with a body weight below 40 kg but who are over 12 years of age the recommended initial and maintenance dose is 62.5 mg twice daily. There is limited information about the safety and efficacy of Tracleer in children between the ages of 12 and 18 years.

Use with Ritonavir

Co-administration of Tracleer in Patients on Ritonavir

In patients who have been receiving ritonavir for at least 10 days, start Tracleer at 62.5 mg once daily or every other day based upon individual tolerability [see **Drug Interactions**].

Co-administration of Ritonavir in Patients on Tracleer

Discontinue use of Tracleer at least 36 hours prior to initiation of ritonavir. After at least 10 days following the initiation of ritonavir, resume Tracleer at 62.5 mg once daily or every other day based upon individual tolerability [see **Dosage and Administration** and **Drug Interactions**].

Treatment Discontinuation

There is limited experience with abrupt discontinuation of Tracleer. No evidence for acute rebound has been observed. Nevertheless, to avoid the potential for clinical deterioration, gradual dose reduction (62.5 mg twice daily for 3 to 7 days) should be considered.

DOSAGE FORMS AND STRENGTHS

Tracleer is available as 62.5 mg and 125 mg film-coated, unscored tablets for oral administration.

62.5 mg tablets: film-coated, round, biconvex, orange-white tablets, embossed with identification marking "62,5"

125 mg tablets: film-coated, oval, biconvex, orange-white tablets, embossed with identification marking "125"

CONTRAINDICATIONS

Pregnancy Category X *[see BOXED WARNING]*

Use of Tracleer is contraindicated in females who are or may become pregnant. While there are no adequate and well controlled studies in pregnant females, animal studies show that Tracleer is likely to cause major birth defects when administered during pregnancy. In animal studies, bosentan caused teratogenic effects including malformations of the head, mouth, face, and large blood vessels. Therefore, pregnancy must be excluded before the start of treatment with Tracleer. Throughout treatment and for one month after stopping Tracleer, females of child bearing potential must use two reliable methods of contraception unless the patient has a tubal sterilization or Copper T 380A IUD or LNg 20 IUS inserted, in which case no other contraception is needed. Monthly pregnancy tests should also be obtained. If this drug is used during pregnancy or if a patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. [see **Use in Specific Populations**].

Use with Cyclosporine A

Co-administration of cyclosporine A and bosentan resulted in markedly increased plasma concentrations of bosentan. Therefore, concomitant use of Tracleer and cyclosporine A is contraindicated [see **Drug Interactions**].

Use with Glyburide

An increased risk of liver enzyme elevations was observed in patients receiving glyburide concomitantly with bosentan. Therefore co-administration of glyburide and Tracleer is contraindicated [see **Drug Interactions**].

Hypersensitivity

Tracleer is contraindicated in patients who are hypersensitive to bosentan or any component of the product. Observed reactions include rash and angioedema [see **Adverse Reactions**].

WARNINGS AND PRECAUTIONS

Potential Liver Injury

Elevations in ALT or AST by more than 3 x ULN were observed in 11% of bosentan-treated patients (N = 658) compared to 2% of placebo-treated patients (N = 280). Three-fold increases were seen in 12% of 95 pulmonary arterial hypertension (PAH) patients on 125 mg twice daily and 14% of 70 PAH patients on 250 mg twice daily. Eight-fold increases were seen in 2% of PAH patients on 125 mg twice daily and 7% of PAH patients on 250 mg twice daily. Bilirubin increases to ≥3 x ULN were associated with aminotransferase increases in 2 of 658 (0.3%) of patients treated with bosentan. The combination of hepatocellular injury (increases in aminotransferases of > 3 x ULN) and increases in total bilirubin (≥ 3 x ULN) is a marker for potential serious liver injury.

Elevations of AST and/or ALT associated with bosentan are dose-dependent, occur both early and late in treatment, usually progress slowly, are typically asymptomatic, and usually have been reversible after treatment interruption or cessation. Aminotransferase elevations also may reverse spontaneously while continuing treatment with Tracleer.

Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥ 2 x ULN, treatment should be stopped. There is no experience with the re-introduction of Tracleer in these circumstances [see **Dosage and Administration**].

Patients with Pre-existing Hepatic Impairment

Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. Tracleer should generally be avoided in patients with moderate or severe liver impairment [see **Dosage and Administration**]. In addition, Tracleer should generally be avoided in patients with elevated aminotransferases (> 3 x ULN) because monitoring liver injury in these patients may be more difficult [see **Boxed Warning**].

Fluid Retention

Peripheral edema is a known clinical consequence of PAH and worsening PAH and is also a known effect of other endothelin receptor antagonists. In PAH clinical trials with Tracleer, combined adverse events of fluid retention or edema were reported in 1.7 percent (placebo-corrected) of patients [see **Clinical Studies**].

In addition, there have been numerous post-marketing reports of fluid retention in patients with pulmonary hypertension occurring within weeks after starting Tracleer. Patients required intervention with a diuretic, fluid management, or hospitalization for decompensating heart failure.

If clinically significant fluid retention develops, with or without associated weight gain, further evaluation should be undertaken to determine the cause, such as Tracleer or underlying heart failure, and the possible need for treatment or discontinuation of Tracleer therapy.

Decreased Sperm Counts

An open-label, single arm, multicenter, safety study evaluated the effect on testicular function of Tracleer 62.5 mg twice daily for 4 weeks, followed by 125 mg twice daily for 5 months. Twenty-five male patients with WHO functional class III and IV PAH and normal baseline sperm count were enrolled. Twenty-three completed the study and 2 discontinued due to adverse events not related to testicular function. There was a decline in sperm count of at least 50% in 25% of the patients after 3 or 6 months of treatment with Tracleer. Sperm count remained within the normal range in all 22 patients with data after 6 months and no changes in sperm morphology, sperm motility, or hormone levels were observed. One patient developed marked oligospermia at 3 months and the sperm count remained low with 2 follow-up measurements over the subsequent 6 weeks. Tracleer was discontinued and after two months the sperm count had returned to baseline levels. Based on these findings and preclinical data from endothelin receptor antagonists, it cannot be excluded that endothelin receptor antagonists such as Tracleer have an adverse effect on spermatogenesis.

Decreases in Hemoglobin and Hematocrit

Treatment with Tracleer can cause a dose-related decrease in hemoglobin and hematocrit. It is recommended that hemoglobin concentrations be checked after 1 and 3 months, and every 3 months thereafter. If a marked decrease in hemoglobin concentration occurs, further evaluation should be undertaken to determine the cause and need for specific treatment.

The overall mean decrease in hemoglobin concentration for bosentan-treated patients was 0.9 g/dL (change to end of treatment). Most of this decrease of hemoglobin concentration was detected during the first few weeks of bosentan treatment and hemoglobin levels stabilized by 4–12 weeks of bosentan treatment. In placebo-controlled studies of all uses of bosentan, marked decreases in hemoglobin (> 15% decrease from baseline resulting in values < 11 g/dL) were observed in 6% of bosentan-treated patients and 3% of placebo-treated patients. In patients with PAH treated with doses of 125 and 250 mg twice daily, marked decreases in hemoglobin occurred in 3% compared to 1% in placebo-treated patients.

A decrease in hemoglobin concentration by at least 1 g/dL was observed in 57% of bosentan-treated patients as compared to 29% of placebo-treated patients. In 80% of those patients whose hemoglobin decreased by at least 1 g/dL, the decrease occurred during the first 6 weeks of bosentan treatment.

During the course of treatment the hemoglobin concentration remained within normal limits in 68% of bosentan-treated patients compared to 76% of placebo patients. The explanation for the change in hemoglobin is not known, but it does not appear to be hemorrhage or hemolysis.

Pulmonary Veno-Occlusive Disease

Should signs of pulmonary edema occur when Tracleer is administered, the possibility of associated pulmonary veno-occlusive disease should be considered and Tracleer should be discontinued.

Prescribing and Distribution Program for Tracleer

Because of the risks of liver injury and birth defects, Tracleer is available only through a special restricted distribution program called the Tracleer Access Program (T.A.P.). Only prescribers and pharmacies registered with T.A.P. may prescribe and distribute Tracleer. In addition, Tracleer may be dispensed only to patients who are enrolled in and meet all conditions of T.A.P. Information about Tracleer and T.A.P. can be obtained by calling 1-866-228-3546.

To enroll in T.A.P., prescribers must complete the T.A.P. Tracleer (bosentan) Enrollment and Renewal Form (see T.A.P. Tracleer (bosentan) Enrollment and Renewal Form for full prescribing physician agreement) indicating agreement to:

- Read and understand the communication and educational materials for prescribers regarding the risks of Tracleer.
- Review and discuss the Tracleer Medication Guide and the risks of bosentan (including the risks of teratogenicity and hepatotoxicity) with every patient prior to prescribing Tracleer.
- Review pretreatment liver function tests (ALT/AST/bilirubin) and, for females of childbearing potential, confirm that the patient is not pregnant.
- Agree to order and monitor monthly liver function tests and, for females of childbearing potential, pregnancy tests.
- Enroll all patients in T.A.P. and renew patients' enrollment annually thereafter.
- Educate and counsel females of childbearing potential to use reliable contraception, as defined on the Tracleer Enrollment and Renewal Form, during treatment with Tracleer and for one month after treatment discontinuation.
- Counsel patients who fail to comply with the program requirements.
- Notify Actelion Pharmaceuticals US, Inc. of any adverse events, including liver injury, and report any pregnancy during Tracleer treatment.

Throughout treatment and for one month after stopping Tracleer, females of childbearing potential must use two reliable methods of contraception unless the patient has a tubal sterilization or Copper T 380A IUD or LNg 20 IUS inserted, in which case no other contraception is needed. Hormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives should not be used as the sole means of contraception because these may not be effective in patients receiving Tracleer.

ADVERSE REACTIONS

The following important adverse reactions are described elsewhere in the labeling:

Potential liver injury [see **Boxed Warning, Warnings and Precautions**]

Fluid retention [see **Warnings and Precautions**]

Clinical Studies Experience

Safety data on bosentan were obtained from 13 clinical studies (9 placebo-controlled and 4 open-label) in 870 patients with pulmonary arterial hypertension and other diseases. Doses up to 8 times the currently recommended clinical dose (125 mg twice daily) were administered for a variety of durations. The exposure to bosentan in these trials ranged from 1 day to 4.1 years (N=94 for 1 year; N=61 for 1.5 years and N=39 for more than 2 years). Exposure of pulmonary arterial hypertension patients (N=328) to bosentan ranged from 1 day to 1.7 years (N=174 more than 6 months and N=28 more than 12 months).

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.

Treatment discontinuations due to adverse events other than those related to pulmonary hypertension during the clinical trials in patients with pulmonary arterial hypertension were more frequent on bosentan (6%; 15/258 patients) than on placebo (3%; 5/172 patients). In this database the only cause of discontinuations > 1% and occurring more often on bosentan was abnormal liver function.

The adverse drug events that occurred in ≥3% of the bosentan-treated patients and were more common on bosentan in placebo-

controlled trials in pulmonary arterial hypertension at doses of 125 or 250 mg twice daily are shown in Table 2:

Adverse events* occurring in ≥3% of patients treated with bosentan 125-250 mg twice daily and more common on bosentan in placebo-controlled studies in pulmonary arterial hypertension

Adverse Event	Bosentan N=258		Placebo N=172	
	No.	%	No.	%
Respiratory Tract Infection	56	22%	30	17%
Headache	39	15%	25	14%
Edema	28	11%	16	9%
Chest Pain	13	5%	8	5%
Syncope	12	5%	7	4%
Flushing	10	4%	5	3%
Hypotension	10	4%	3	2%
Sinusitis	9	4%	4	2%
Arthralgia	9	4%	3	2%
Liver Function Test Abnormal	9	4%	3	2%
Palpitations	9	4%	3	2%
Anemia	8	3%	–	

*Note: only AEs with onset from start of treatment to 1 calendar day after end of treatment are included. All reported events (at least 3%) are included except those too general to be informative, and those not reasonably associated with the use of the drug because they were associated with the condition being treated or are very common in the treated population.

Combined data from Study-351, BREATHE-1 and EARLY

Postmarketing Experience

There have been several post-marketing reports of angioedema associated with the use of bosentan. The onset of the reported cases occurred within a range of 8 hours to 21 days after starting therapy. Some patients were treated with an antihistamine and their signs of angioedema resolved without discontinuing Tracleer.

The following additional adverse reactions have been reported during the post approval use of Tracleer. Because these adverse reactions are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Tracleer exposure:

- Unexplained hepatic cirrhosis [see **Boxed Warning**]
- Liver failure [see **Boxed Warning**]
- Hypersensitivity [see **Contraindications**]
- Thrombocytopenia
- Rash
- Jaundice
- Anemia requiring transfusion
- Neutropenia and leukopenia

DRUG INTERACTIONS

Cytochrome P450 Summary

Bosentan is metabolized by CYP2C9 and CYP3A. Inhibition of these enzymes may increase the plasma concentration of bosentan (see ketoconazole). Concomitant administration of both a CYP2C9 inhibitor (such as fluconazole or amiodarone) and a strong CYP3A inhibitor (e.g., ketoconazole, itraconazole) or a moderate CYP3A inhibitor (e.g., amprenavir, erythromycin, fluconazole, diltiazem) with bosentan will likely lead to large increases in plasma concentrations of bosentan. Co-administration of such combinations of a CYP2C9 inhibitor plus a strong or moderate CYP3A inhibitor with Tracleer is not recommended.

Bosentan is an inducer of CYP3A and CYP2C9. Consequently plasma concentrations of drugs metabolized by these two isozymes will be decreased when Tracleer is co-administered. Bosentan had no relevant inhibitory effect on any CYP isozyme in vitro (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A). Consequently, Tracleer is not expected to increase the plasma concentrations of drugs metabolized by these enzymes.

Hormonal Contraceptives

Hormonal contraceptives, including oral, injectable, transdermal, and implantable forms, may not be reliable when Tracleer is co-administered. Females should practice additional methods of contraception and not rely on hormonal contraception alone when taking Tracleer [see **Boxed Warning, Contraindications**].

An interaction study demonstrated that co-administration of bosentan and a combination oral hormonal contraceptive produced average decreases of norethindrone and ethinyl estradiol levels of 14% and 31%, respectively. However, decreases in exposure were as much as 56% and 66%, respectively, in individual subjects.

Cyclosporine A

The concomitant administration of bosentan and cyclosporine A is contraindicated [see **Contraindications**].

During the first day of concomitant administration, trough concentrations of bosentan were increased by about 30-fold. The mechanism of this interaction is most likely inhibition of transport protein-mediated uptake of bosentan into hepatocytes by cyclosporine. Steady-state bosentan plasma concentrations were 3- to 4-fold higher than in the absence of cyclosporine A. Co-administration of bosentan decreased the plasma concentrations of cyclosporine A (a CYP3A substrate) by approximately 50%.

Glyburide

An increased risk of elevated liver aminotransferases was observed in patients receiving concomitant therapy with glyburide. Therefore, the concomitant administration of Tracleer and glyburide is contraindicated, and alternative hypoglycemic agents should be considered [see **Contraindications**].

Co-administration of bosentan decreased the plasma concentrations of glyburide by approximately 40%. The plasma concentrations of bosentan were also decreased by approximately 30%. Bosentan is also expected to reduce plasma concentrations of other oral hypoglycemic agents that are predominantly metabolized by CYP2C9 or CYP3A. The possibility of worsened glucose control in patients using these agents should be considered.

Lopinavir/Ritonavir or Other Ritonavir-containing HIV Regimens

In vitro data indicate that bosentan is a substrate of the Organic Anion Transport Protein (OATP), CYP3A and CYP2C9. Ritonavir inhibits OATP and inhibits and induces CYP3A. However, the impact of ritonavir on the pharmacokinetics of bosentan may largely result from its effect on OATP.

In normal volunteers, co-administration of Tracleer 125 mg twice daily and lopinavir/ritonavir 400/100 mg twice daily increased the trough concentrations of bosentan on Days 4 and 10 approximately 48-fold and 5-fold, respectively, compared with those measured after Tracleer administered alone. Therefore, adjust the dose of Tracleer when initiating lopinavir/ritonavir [see **Dosage and Administration**].

Co-administration of Tracleer 125 mg twice daily had no substantial impact on the pharmacokinetics of lopinavir/ritonavir 400/100 mg twice daily.

Simvastatin and Other Statins

Co-administration of bosentan decreased the plasma concentrations of simvastatin (a CYP3A substrate), and its active β-hydroxy acid metabolite, by approximately 50%. The plasma concentrations of bosentan were not affected. Bosentan is also expected to reduce plasma concentrations of other statins that are significantly metabolized by CYP3A, such as lovastatin and atorvastatin. The possibility of reduced statin efficacy should be considered. Patients using CYP3A-metabolized statins should have cholesterol levels monitored after Tracleer is initiated to see whether the statin dose needs adjustment.

Rifampin

Co-administration of bosentan and rifampin in normal volunteers resulted in a mean 6-fold increase in bosentan trough levels after the first concomitant dose (likely due to inhibition of OATP by rifampin), but about a 60% decrease in bosentan levels at steady-state. The effect of bosentan on rifampin levels has not been assessed. When consideration of the potential benefits and known and unknown risks leads to concomitant use, measure liver function weekly for the first 4 weeks before reverting to normal monitoring.

Tacrolimus

Co-administration of tacrolimus and bosentan has not been studied in humans. Co-administration of tacrolimus and bosentan resulted in markedly increased plasma concentrations of bosentan in animals. Caution should be exercised if tacrolimus and bosentan are used together.

Ketoconazole

Co-administration of bosentan 125 mg twice daily and ketoconazole, a potent CYP3A inhibitor, increased the plasma concentrations of bosentan by approximately 2-fold in normal volunteers. No dose adjustment of bosentan is necessary, but increased effects of bosentan should be considered.

Warfarin

Co-administration of bosentan 500 mg twice daily for 6 days in normal volunteers, decreased the plasma concentrations of both S-warfarin (a CYP2C9 substrate) and R-warfarin (a CYP3A substrate) by 29 and 38%, respectively. Clinical experience with concomitant administration of bosentan and warfarin in patients with pulmonary arterial hypertension did not show clinically relevant changes in INR or warfarin dose (baseline vs. end of the clinical studies), and the need to change the warfarin dose during the trials due to changes in INR or due to adverse events was similar among bosentan- and placebo-treated patients.

Digoxin, Nimodipine, and Losartan

Bosentan has no significant pharmacokinetic interactions with digoxin and nimodipine, and losartan has no significant effect on plasma levels of bosentan.

Sildenafil

In normal volunteers, co-administration of multiple doses of 125 mg twice daily bosentan and 80 mg three times daily sildenafil resulted in a reduction of sildenafil plasma concentrations by 63% and increased bosentan plasma concentrations by 50%. The changes in plasma concentrations were not considered clinically relevant and dose adjustments are not necessary. This recommendation holds true when sildenafil is used for the treatment of pulmonary arterial hypertension or erectile dysfunction.

Iloprost

In a small, randomized, double-blind, placebo-controlled study, 34 patients treated with bosentan 125 mg twice daily for at least 16 weeks tolerated the addition of inhaled iloprost (up to 5 mcg 6 to 9 times per day during waking hours). The mean daily inhaled dose was 27 mcg and the mean number of inhalations per day was 5.6.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category X: Teratogenic Effects [see Contraindications]

Use of Tracleer is contraindicated in females who are or may become pregnant. While there are no adequate and well controlled studies in pregnant females, animal studies show that Tracleer is likely to cause major birth defects when administered during pregnancy. Bosentan caused teratogenic effects in animals including malformations of the head, mouth, face, and large blood vessels. If this drug is used during pregnancy or if a patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Females of childbearing potential should have a negative pregnancy test before starting treatment with Tracleer. The prescriber should not dispense a prescription for Tracleer without documenting a negative urine or serum pregnancy test performed during the first 5 days of a normal menstrual period and at least 11 days after the last unprotected act of sexual intercourse. Follow-up urine or serum pregnancy tests should be obtained monthly in females of childbearing potential taking Tracleer. The patient should contact her physician immediately for pregnancy testing if onset of menses is delayed or pregnancy is suspected. If the pregnancy test is positive, the physician and patient must discuss the risks to her, the pregnancy, and the fetus.

Drug interaction studies show that Tracleer reduces serum levels of the estrogen and progestin in oral contraceptives. Based on these findings, hormonal contraceptives (including oral, injectable, transdermal, and implantable contraceptives) may be less effective for preventing pregnancy in patients using Tracleer and should not be used as a patient's only contraceptive method [see **Drug Interactions**]. Females of childbearing potential using Tracleer must use two reliable forms of contraception unless she has a tubal sterilization or has a Copper T 380A IUD or LNg 20 IUS. In these cases, no additional contraception is needed. Contraception should be continued until one month after completing Tracleer therapy. Females of childbearing potential using Tracleer should seek contraception counseling from a gynecologist or other expert as needed.

Bosentan was teratogenic in rats given oral doses two times the maximum recommended human dose [MRHD] (on a mg/ m^2 basis). In an embryo-fetal toxicity study in rats, bosentan showed dose-dependent teratogenic effects, including malformations of the head, mouth, face and large blood vessels. Bosentan increased stillbirths and pup mortality at oral doses 2 and 10 times the MRHD (on a mg/m^2 basis). Although birth defects were not observed in rabbits given oral doses of up to the equivalent of 10.5 g/day in a 70 kg person, plasma concentrations of bosentan in rabbits were lower than those reached in the rat. The similarity of malformations induced by bosentan and those observed in endothelin-1 knockout mice and in animals treated with other endothelin receptor antagonists indicates that teratogenicity is a class effect of these drugs [see **Nonclinical Toxicology**].

Nursing mothers

It is not known whether Tracleer is excreted into human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from Tracleer, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric use

Safety and efficacy in pediatric patients have not been established.

Geriatric use

Clinical studies of Tracleer did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. Clinical experience has not identified differences in responses between elderly and younger patients. In general, caution should be exercised in dose selection for elderly patients given the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this age group.

Hepatic Impairment

Because there is *in vitro* and *in vivo* evidence that the main route of excretion of bosentan is biliary, liver impairment could be expected to increase exposure (C_{max} and AUC) of bosentan. Mild liver impairment was shown not to impact the pharmacokinetics of bosentan. The influence of moderate or severe liver impairment on the pharmacokinetics of Tracleer has not been evaluated. There are no specific data to guide dosing in hepatically impaired patients; caution should be exercised in patients with mildly impaired liver function. Tracleer should generally be avoided in patients with moderate or severe liver impairment [see **Dosage and Administration, Warnings and Precautions**].

Renal Impairment

The effect of renal impairment on the pharmacokinetics of bosentan is small and does not require dosing adjustment.

Patients with Low Body Weight [See Dosage and Administration].

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carinogenesis and Mutagenesis

Two years of dietary administration of bosentan to mice produced an increased incidence of hepatocellular adenomas and carcinomas in males at doses as low as 450 mg/kg/day (about 8 times the maximum recommended human dose [MRHD] of 125 mg twice daily, on a mg/m^2 basis). In the same study, doses greater than 2000 mg/kg/day (about 32 times the MRHD) were associated with an increased incidence of colon adenomas in both males and females. In rats, dietary administration of bosentan for two years was associated with an increased incidence of brain astrocytomas in males at doses as low as 500 mg/kg/day (about 16 times the MRHD). In a comprehensive battery of *in vitro* tests (the microbial mutagenesis assay, the unscheduled DNA synthesis assay, the V-79 mammalian cell mutagenesis assay, and human lymphocyte assay) and an *in vivo* mouse micronucleus assay, there was no evidence for any mutagenic or clastogenic activity of bosentan.

Reproductive and Developmental Toxicology

Bosentan was teratogenic in rats given oral doses ≥60 mg/kg/day. In an embryo-fetal toxicity study in rats, bosentan showed dose-dependent teratogenic effects, including malformations of the head, mouth, face and large blood vessels. Bosentan increased stillbirths and pup mortality at oral doses of 60 and 300 mg/kg/day. Although birth defects were not observed in rabbits given oral doses of up to 1500 mg/kg/day, plasma concentrations of bosentan in rabbits were lower than those reached in the rat. The similarity of malformations induced by bosentan and those observed in endothelin-1 knockout mice and in animals treated with other endothelin receptor antagonists indicates that teratogenicity is a class effect of these drugs.

Impairment of Fertility/Testicular Function

The development of testicular tubular atrophy and impaired fertility has been linked with the chronic administration of certain endothelin receptor antagonists in rodents.

Treatment with bosentan at oral doses of up to 1500 mg/kg/day (50 times the MRHD on a mg/m^2 basis) or intravenous doses up to 40 mg/kg/day had no effects on sperm count, sperm motility, mating performance or fertility in male and female rats. An increased incidence of testicular tubular atrophy was observed in rats given bosentan orally at doses as low as 125 mg/kg/day (about 4 times the MRHD and the lowest doses tested) for two years but not at doses as high as 1500 mg/kg/day (about 50 times the MRHD) for 6 months. Effects on sperm count and motility were evaluated only in the much shorter duration fertility studies in which males had been exposed to the drug for 4-6 weeks. An increased incidence of tubular atrophy was not observed in mice treated for 2 years at doses up to 4500 mg/kg/day (about 75 times the MRHD) or in dogs treated up to 12 months at doses up to 500 mg/kg/day (about 50 times the MRHD).

PATIENT COUNSELING INFORMATION

Advise patients to consult the Medication Guide on the safe use of Tracleer.

Important Information

- Monthly monitoring of serum aminotransferases

The physician should discuss with the patient the importance of monthly monitoring of serum aminotransferases.

- Pregnancy testing and avoidance of pregnancy

Patients should be advised that Tracleer is likely to cause birth defects based on animal studies. Tracleer treatment should only be initiated in females of childbearing potential following a negative pregnancy test. Females of childbearing potential must have monthly pregnancy tests and need to use two different forms of contraception while taking Tracleer and for one month after discontinuing Tracleer. Females who have a tubal ligation or a Copper T 380A IUD or LNg 20 IUS can use these contraceptive methods alone. Patients should be instructed to immediately contact their physician if they suspect they may be pregnant and should seek contraceptive advice from a gynecologist or similar expert as needed.

- Drug Interactions

The physician should discuss with the patient possible drug interactions with Tracleer, and which medications should not be taken with Tracleer. The physician should discuss the importance of disclosing all concomitant or new medications.

Manufactured for: Actelion Pharmaceuticals US, Inc. South San Francisco, CA 94080, USA
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References for previous pages: 1. Data on file, Actelion Pharmaceuticals.

ACTELION

Pulmonary Perspectives

HIV-Associated Pulmonary Arterial Hypertension

Screening for HIV-associated PAH is important to ensure early intervention.

Data from the Centers for Disease Control and Prevention indicate that approximately 1 million persons in the United States are living with HIV and more than 18,000 persons with AIDS die each year. Pulmonary diseases account for a large percentage of HIV-related complications and pulmonary arterial hypertension (PAH) is a noninfectious complication of HIV infection (Morris et al. *Proc Am Thorac Soc.* 2011;8[1]:17). PAH is reported to occur at an increased frequency in HIV-infected individuals compared with uninfected individuals.

HIV-associated PAH (HAPAH) is more prevalent in men and IV drug users. Though the prevalence of HAPAH has remained at 0.5% before and after the introduction of antiretroviral therapy (Sitbon et al. *Am J Respir Crit Care Med.* 2008;177[1]:108), the incidence of HAPAH appears to be increasing as antiretroviral therapy prolongs survival in patients with HIV. Speculation that preclinical HAPAH may be more common than recognized is supported by the finding that 35% of HIV-infected individuals had pulmonary artery systolic pressures over 30 mm Hg on screening echocardiography (Hsue et al. *AIDS*. 2008;22[7]:825). Identifying and treating persons with HAPAH is important because the mortality is higher compared with normotensive patients with HIV (Almodovar et al. *Chest*. 2010;137[6]:6S).

The clinical and pathologic features of PAH are identical in HIV-infected patients and noninfected individuals. The presentation includes nonspecific symptoms of dyspnea, fatigue, nonproductive cough, chest pain, and syncope. Patients with HAPAH have increased proliferation of endothelial and smooth muscle cells with medial hypertrophy and obliteration of the pulmonary vessels (Petitpretz et al. *Circulation*. 1994;89[6]:2722). Plexiform lesions are seen in 78% of patients with HAPAH (Mehta et al. *Chest*. 2000;118[4]:1133). The pathogenesis of HAPAH is poorly understood. It is uncertain whether the virus has a direct effect on endothelial cells, as there is no evidence that HIV directly infects pulmonary vascular endothelial cells. However, HIV viral antigens are seen in the pulmonary endothelium and may be responsible for stimulating abnormal apoptosis, growth, and proliferation of cells. HIV viral antigens under investigation include glycoprotein 120, negative factor (Nef) antigen, and HIV-1 tat (transcriptional transactivator). Human herpes virus-8 (HHV-8) has also been investigated but has not been conclusively demonstrated to play a role in the development of HAPAH. In an animal model of simian immunodeficiency virus, primates expressing HIV Nef are noted to develop lesions similar to the plexiform lesions seen in PAH (Marecki et al. *Am J Respir Crit Care Med*. 2006;174[4]:437). In vitro, Nef antigen causes increased apoptosis followed by proliferation of human endothelial cells (Marecki et al. *Proc Am Thorac Soc*. 2006;3:A476).

Other pathways by which HIV may play a role in the pathogenesis of PAH include mechanisms related to the chronic inflammation associated with HIV. Lung tissue from patients with HAPAH has been noted to show an increase in the expression of platelet-derived growth factor, a potent stimulus of growth and migration in fibroblasts and smooth muscle cells (Humbert et al. *Eur Respir J*. 1998;11[3]:554). There is no correlation between HAPAH and CD4 cell count or viral load (Nunes et al. *Am J Respir Crit Care Med*. 2003;167[10]:1433; Humbert et al. *Am J Respir Crit Care Med*. 2006;173[9]:1023).

Few studies have investigated therapeutic options for HAPAH. The role of antiretroviral therapy in the development and progression of HAPAH is controversial. Although some studies demonstrate a benefit for highly active antiretroviral therapy (HAART) in HAPAH, other studies show no benefit. Zuber and colleagues (Zuber et al. Clin Infect Dis. 2004; 38[8]:1178) demonstrated an improvement in hemodynamics and survival in patients with HAPAH treated with antiretrovirals, but their findings were limited in that the diagnosis of PAH was made by echocardiography rather than right-sided heart catheterization. Speich and coworkers (Speich et al. *Swiss Med Wkly*. 2001;131[45-46]:663) reported a case where the subject, who had a history of cocaine use, was noted to have regression of PAH while receiving antiretroviral therapy with an increase in survival to 6 years compared with the then-typical 3-year survival following diagnosis of HAPAH. In a case-control study where Opravil and colleagues (Opravil et al. *Am J Respir Crit Care Med*. 1997;155[3]:990) compared HIV patients with PAH to those without PAH, a statistically significant decrease of 3.2 mm Hg in the right ventricular systolic pressure–right atrial pressure (RVSP-RAP) gradient was noted in the six patients receiving antiretroviral therapy, while this gradient increased by 19 mm Hg in untreated patients. In contrast, a study published by Reinsch and colleagues (Reinsch et al. *HIV Medicine*. 2008;9[7]:550) showed that patients with HIV receiving HAART had a slight increase in systolic pulmonary arterial pressure. Comparatively, Pugliese and colleagues (Pugliese et al. *J Infect*. 2000;40[3]:282) reported that the incidence of PAH was increased in HIV-infected patients receiving HAART compared with those receiving nucleoside reverse transcriptase inhibitors.

Treatment options for HAPAH are limited. Calcium channel blockers, effective in treating PAH in patients who are responsive to vasodilator challenge, tend to be ineffective in HAPAH. Epoprostenol has been shown to improve hemodynamics and functional status in patients with HAPAH. Acute infusion of epoprostenol reduces mean pulmonary artery pressure (PAP).

Long-term changes noted with epoprostenol therapy include a fall in PAP and peripheral vascular resistance with an increase in cardiac output and cardiac index. The NYHA functional class of patients with HAPAH was noted to improve significantly in patients receiving long-term epoprostenol (Aguilar and Farber. *Am J Respir Crit Care Med*. 2000;162[5]:1846). Side effects of epoprostenol were similar to those seen in non-HIV-infected patients undergoing treatment for PAH, including jaw pain, headache, and flushing.

A small study suggests that inhaled iloprost reduces pulmonary vascular resistance, increases cardiac output, and improves exercise capacity in patients with HAPAH (Ghofrani et al. *Eur Respir J*. 2004;23[2]:321).

Bosentan therapy has been shown to improve 6-min walk distance, hemodynamics, and quality of life in patients with HAPAH without having a negative impact on the control of HIV infection, as CD4 cell count and viral load were not affected (Sitbon et al. *Am J Respir Crit Care Med*. 2004;170[11]:1212; Degano et al. *Eur Respir J*. 2009;33[1]:92). Barbaro and colleagues (Barbaro et al. *Heart*. 2006; 92[8]:1164) reported that HAART combined with bosentan, compared with HAART alone, reduced PAP by 21% and reduced pulmonary capillary wedge pressure by 12%. The combination of HAART and bosentan appeared to be safe, without negatively impacting the control of the HIV infection.

Sildenafil was noted to cause a rapid improvement in the patient's dyspnea and symptoms of right-sided heart failure in a case report published by Alp and coworkers (Alp et al. *AIDS*. 2003;17[11]:1714). Schumacher and colleagues (Schumacher et al. *AIDS*. 2001;15[11]:1747) reported a similar case in which a patient, after 3 months of follow-up, was observed to have a decrease in PAP estimated from echocardiography with an associated improvement in dyspnea and exercise capacity.

With regards to prognostic indicators, multivariate analysis of patients with HAPAH in NYHA functional class III-IV showed that the CD4 lymphocyte count was the only independent predictor of survival. Univariate analysis of the same study population revealed that a CD4 lymphocyte count over 212 cells/mm^3, use of combination antiretroviral therapy, and epoprostenol therapy were significantly associated with a decreased risk of death (Nunes et al. *Am J Respir Crit Care Med*. 2003;167[10]:1433).

Screening for HAPAH is important to ensure early intervention. Additional studies are needed to further elucidate the pathogenesis of PAH in patients with HIV so that potential treatment targets may be identified. ■

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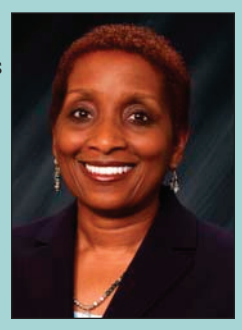
Editor's Insight



Recent innovations and advances in medical care that have prolonged the survival of individuals with HIV infection has led to an expectation that these individuals will lead longer and fuller lives. Concurrently, significant progress has also been made in the treatment of pulmonary arterial hypertension. This update of HIV-associated PAH should lead us to consider a diagnosis of PAH in HIV-infected individuals with, among other symptoms, unexplained dyspnea.

–Dr. Marilyn G. Foreman, FCCP

For the treatment of adults with community-acquired bacterial pneumonia ***(CABP)*** *and acute bacterial skin and skin structure infections* ***(ABSSSI)*** *caused by designated susceptible bacteria, as indicated below*

Discover a NEW IV Cephalosporin for

COMMUNITY-ACQUIRED BACTERIAL PNEUMONIA

CABP

A

D

ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS

ABSSSI

INDICATIONS

- TEFLARO™ is indicated for the treatment of **community-acquired bacterial pneumonia (CABP)** caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Streptococcus pneumoniae* (including cases with concurrent bacteremia), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Escherichia coli*.
- TEFLARO is also indicated for the treatment of **acute bacterial skin and skin structure infections (ABSSSI)** caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*.

IMPORTANT SAFETY INFORMATION

Contraindications

- TEFLARO is contraindicated in patients with known serious hypersensitivity to ceftaroline or other members of the cephalosporin class. Anaphylaxis and anaphylactoid reactions have been reported with ceftaroline.

Please see additional Important Safety Information throughout and brief summary of Prescribing Information on last page of this advertisement.

Please also see full Prescribing Information at www.TEFLARO.com.

NEW

Teflaro™

(ceftaroline fosamil) for injection

600 mg • 400 mg

.125 from Trim

Trim Line

Introducing TEFLARO™

BROAD-SPECTRUM cephalosporin coverage

INDICATIONS AND USAGE

- TEFLARO is indicated for the treatment of **community-acquired bacterial pneumonia (CABP)** caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Streptococcus pneumoniae* (including cases with concurrent bacteremia), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Escherichia coli*.
- TEFLARO is also indicated for the treatment of **acute bacterial skin and skin structure infections (ABSSSI)** caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*.
- To reduce the development of drug-resistant bacteria and maintain the effectiveness of TEFLARO and other antibacterial drugs, TEFLARO should be used to treat only ABSSSI or CABP that are proven or strongly suspected to be caused by susceptible bacteria.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Hypersensitivity Reactions

- Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and serious skin reactions have been reported with beta-lactam antibacterials. Before therapy with TEFLARO is instituted, careful inquiry about previous hypersensitivity reactions to other cephalosporins, penicillins, or carbapenems should be made. If this product is to be given to a penicillin- or other beta-lactam-allergic patient, caution should be exercised because cross sensitivity among beta-lactam antibacterial agents has been clearly established.
- If an allergic reaction to TEFLARO occurs, the drug should be discontinued. Serious acute hypersensitivity (anaphylactic) reactions require emergency treatment with epinephrine and other emergency measures that may include airway management, oxygen, intravenous fluids, antihistamines, corticosteroids, and vasopressors as clinically indicated.

Clostridium difficile-associated Diarrhea

- *Clostridium difficile*-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial agents, including TEFLARO, and may range in severity from mild diarrhea to fatal colitis. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents. If CDAD is suspected or confirmed, antibacterials not directed against *C. difficile* should be discontinued, if possible.

Broad-spectrum coverage for treating CABP and ABSSSI

Bactericidal Activity Against a Broad Spectrum of Gram-positive and Gram-negative Pathogens, Including *S. pneumoniae* in CABP and MRSA in ABSSSI[1]

Proven efficacy in 2 common infections
in patients admitted to the hospital[1,2]

CABP | **ABSSSI**

- **Convenient q12h dosing in CABP and ABSSSI[1]**
  - 600 mg intravenous over 1 hour
  - Treatment duration
    - 5-7 days for CABP
    - 5-14 days for ABSSSI

IMPORTANT SAFETY INFORMATION

Direct Coombs' Test Seroconversion

- Seroconversion from a negative to a positive direct Coombs' test result occurred in 120/1114 (10.8%) of patients receiving TEFLARO and 49/1116 (4.4%) of patients receiving comparator drugs in the four pooled Phase 3 trials. No adverse reactions representing hemolytic anemia were reported in any treatment group. If anemia develops during or after treatment with TEFLARO, drug-induced hemolytic anemia should be considered. If drug-induced hemolytic anemia is suspected, discontinuation of TEFLARO should be considered and supportive care should be administered to the patient if clinically indicated.

Development of Drug-Resistant Bacteria

- Prescribing TEFLARO in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Please see additional Important Safety Information throughout and brief summary of Prescribing Information on last page of this advertisement.

NEW
Teflaro™
(ceftaroline fosamil) for injection
600 mg • 400 mg

Demonstrated efficacy in CABP

TEFLARO CABP Study Designs[1,3]

Type of trial: Two randomized, multicenter, multinational, double-blind, noninferiority trials

Study population: 1231 adults with a diagnosis of CABP

Comparative agents: TEFLARO – 600 mg administered IV over 1 hour every 12 hours for 5-7 days;
Ceftriaxone – 1 g ceftriaxone administered IV over 30 minutes every 24 hours for 5-7 days

Adjunctive therapy: CABP Trial 1, two doses on Day 1 of oral clarithromycin 500 mg every 12 hours;
CABP Trial 2, no adjunctive macrolide therapy

TEFLARO Study Populations		
Day 4 Population (mITT)*		A microbiological intent-to-treat population (mITT population) containing only subjects with a confirmed bacterial pathogen at baseline.
Test of Cure (TOC) Populations†		
MITT	Modified Intent-to-treat	All randomized subjects who received any amount of study drug.
MITTE	Modified Intent-to-treat Efficacy	All subjects in the MITT population who were in PORT Risk Class III or IV at baseline.
CE	Clinically Evaluable	All subjects in the MITTE population who demonstrated sufficient adherence to the protocol. Sufficient adherence is defined as patients who met the minimal disease criteria for CABP and for whom sufficient information regarding the CABP was available to determine the patient's outcome.
ME	Microbiologically Evaluable	All subjects in the CE population who had at least one typical bacterial pathogen identified at baseline from an appropriate microbiological specimen (eg, blood, sputum, or pleural fluid).

* To evaluate the treatment effect of ceftaroline, an analysis was conducted in CABP patients for whom the treatment effect of antibacterials may be supported by historical evidence. This analysis endpoint required subjects to meet sign and symptom criteria at Day 4 of therapy: a responder had to both (a) be in stable condition according to consensus treatment guidelines, and (b) show improvement from baseline on at least one symptom of cough, dyspnea, pleuritic chest pain, or sputum production, while not worsening on any of these four symptoms.

† The protocol-specified analyses included clinical cure rates at the TOC (8 to 15 days after the end of therapy) in the coprimary MITTE and CE populations and clinical cure rates at TOC by pathogen in the ME population.

INDICATION AND USAGE

- TEFLARO is indicated for the treatment of **community-acquired bacterial pneumonia (CABP)** caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Streptococcus pneumoniae* (including cases with concurrent bacteremia), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Escherichia coli*.
- To reduce the development of drug-resistant bacteria and maintain the effectiveness of TEFLARO and other antibacterial drugs, TEFLARO should be used to treat only CABP that is proven or strongly suspected to be caused by susceptible bacteria.

IMPORTANT SAFETY INFORMATION

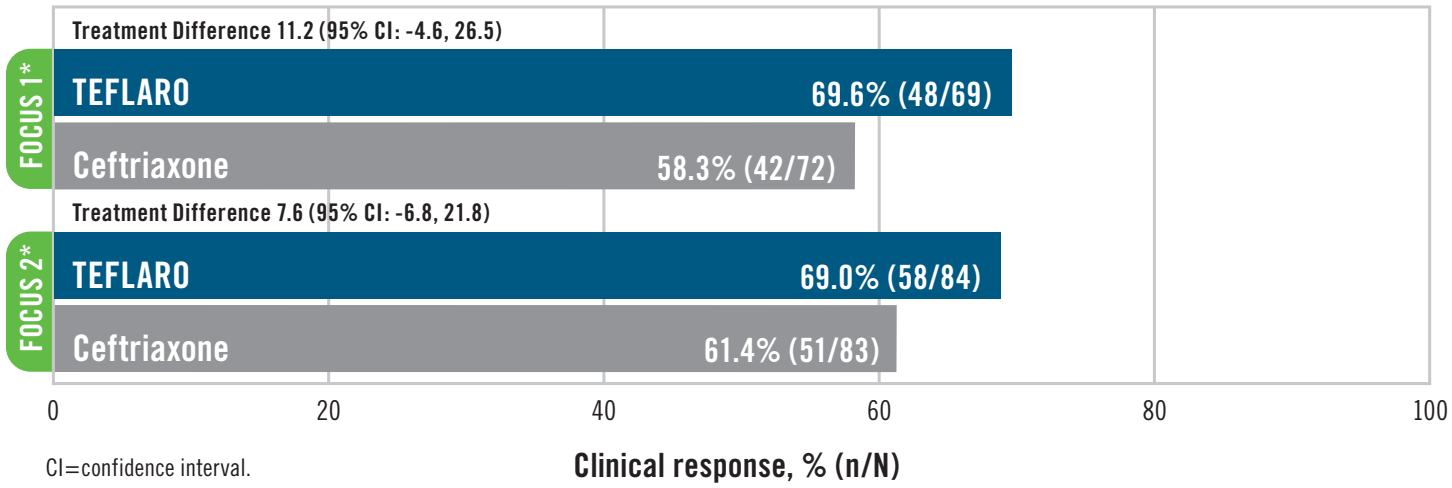
Adverse Reactions

- In the four pooled Phase 3 clinical trials, serious adverse events occurred in 98/1300 (7.5%) of patients receiving TEFLARO and 100/1297 (7.7%) of patients receiving comparator drugs. Treatment discontinuation due to adverse events occurred in 35/1300 (2.7%) of patients receiving TEFLARO and 48/1297 (3.7%) of patients receiving comparator drugs with the most common adverse events leading to discontinuation being hypersensitivity for both treatment groups at a rate of 0.3% in the TEFLARO group and 0.5% in the comparator group.
- No adverse reactions occurred in greater than 5% of patients receiving TEFLARO. The most common adverse reactions occurring in >2% of patients receiving TEFLARO in the pooled Phase 3 clinical trials were diarrhea, nausea, and rash.

Please see additional Important Safety Information throughout and brief summary of Prescribing Information on last page of this advertisement.

CABP

TEFLARO Demonstrated Clinical Response at Day 4 (mITT) in Community-Acquired Bacterial Pneumonia[1]

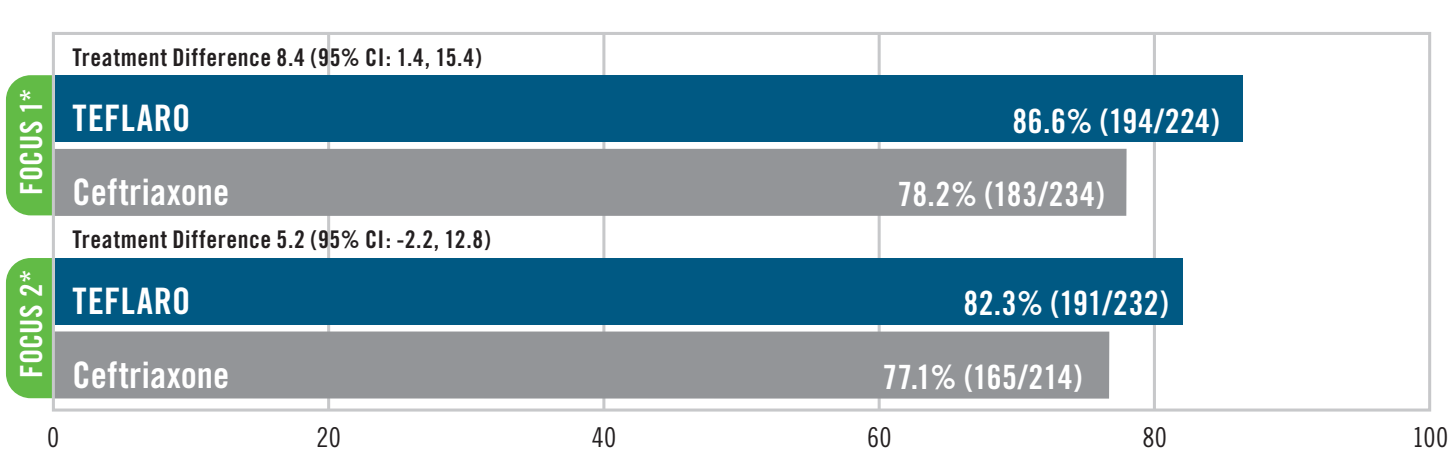


CI=confidence interval.

Neither trial established that TEFLARO was statistically superior to ceftriaxone in terms of clinical response rates.

CABP

TEFLARO Demonstrated Efficacy at TOC† (CE) in Community-Acquired Bacterial Pneumonia[1]



CI=confidence interval.

Neither trial established that TEFLARO was statistically superior to ceftriaxone in terms of clinical response rates.

Patients with known or suspected MRSA were excluded from both trials.

*FOCUS=Ce**f**tar**o**line **C**ommunity-Acquired Pne**u**monia Trial v**s** Ceftriaxone in Hospital Patients. FOCUS 1=CABP Trial 1, FOCUS 2=CABP Trial 2.

†There are insufficient historical data to establish the magnitude of drug effect for antibacterial drugs compared with placebo at a TOC time point. Therefore, comparisons of TEFLARO to ceftriaxone based on clinical response rates at TOC cannot be utilized to establish noninferiority.

IMPORTANT SAFETY INFORMATION

Drug Interactions

- No clinical drug-drug interaction studies have been conducted with TEFLARO. There is minimal potential for drug-drug interactions between TEFLARO and CYP450 substrates, inhibitors, or inducers; drugs known to undergo active renal secretion; and drugs that may alter renal blood flow.

NEW
Teflaro™
(ceftaroline fosamil) for injection
600 mg • 400 mg

Demonstrated efficacy in ABSSSI

TEFLARO ABSSSI Study Design[1,3]

Type of trial: Two identical, randomized, multicenter, multinational, double-blind, noninferiority trials

Study population: 1396 adults with clinically documented complicated skin and skin structure infection

Comparative agents: TEFLARO – 600 mg administered IV over 1 hour every 12 hours for 5-14 days;
Vancomycin plus aztreonam – 1 g vancomycin administered IV over 1 hour followed by 1 g aztreonam administered IV over 1 hour every 12 hours for 5-14 days

Treatment duration: Treatment duration was 5 to 14 days. A switch to oral therapy was not allowed

TEFLARO Study Populations

Day 3 Population*

The analysis evaluated patients with lesion size ≥75 cm^2 and having one of the following infection types:
- Major abscess with ≥5 cm of surrounding erythema
- Wound infection
- Deep/extensive cellulitis

Test of Cure (TOC) Populations†

MITT	Modified Intent-to-treat	All randomized subjects who received any amount of study drug.
CE	Clinically Evaluable	Patients in the MITT population who demonstrated sufficient adherence to the protocol. Sufficient adherence is defined as patients who met the minimal clinical disease criteria for cSSSI and all evaluability criteria, including subjects who received at least the pre-specified minimal amount of the intended dose and duration of study drug therapy, for which sufficient information regarding the cSSSI site is available to determine the subject's outcome, and for which there were no confounding factors that interfered with the assessment of that outcome.
ME	Microbiologically Evaluable	This population consists of a subset of subjects from the CE population who had at least one bacterial pathogen identified from a blood culture or culture of an adequate microbiological sample obtained from the cSSSI site at baseline and who had susceptibility testing performed on at least one of the isolated baseline pathogens.

* To evaluate the treatment effect of ceftaroline, an analysis was conducted in 797 patients with ABSSSI (such as deep/extensive cellulitis or a wound infection [surgical or traumatic]) for whom the treatment effect of antibacterials may be supported by historical evidence. This analysis evaluated responder rates based on achieving both cessation of lesion spread and absence of fever on Trial Day 3.

†The protocol-specified analyses included clinical cure rates at the TOC (8 to 15 days after the end of therapy) in the coprimary CE and MITT populations and clinical cure rates at TOC by pathogen in the ME population.

INDICATION AND USAGE

- TEFLARO is indicated for the treatment of **acute bacterial skin and skin structure infections (ABSSSI)** caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*.
- To reduce the development of drug-resistant bacteria and maintain the effectiveness of TEFLARO and other antibacterial drugs, TEFLARO should be used to treat only ABSSSI that is proven or strongly suspected to be caused by susceptible bacteria.

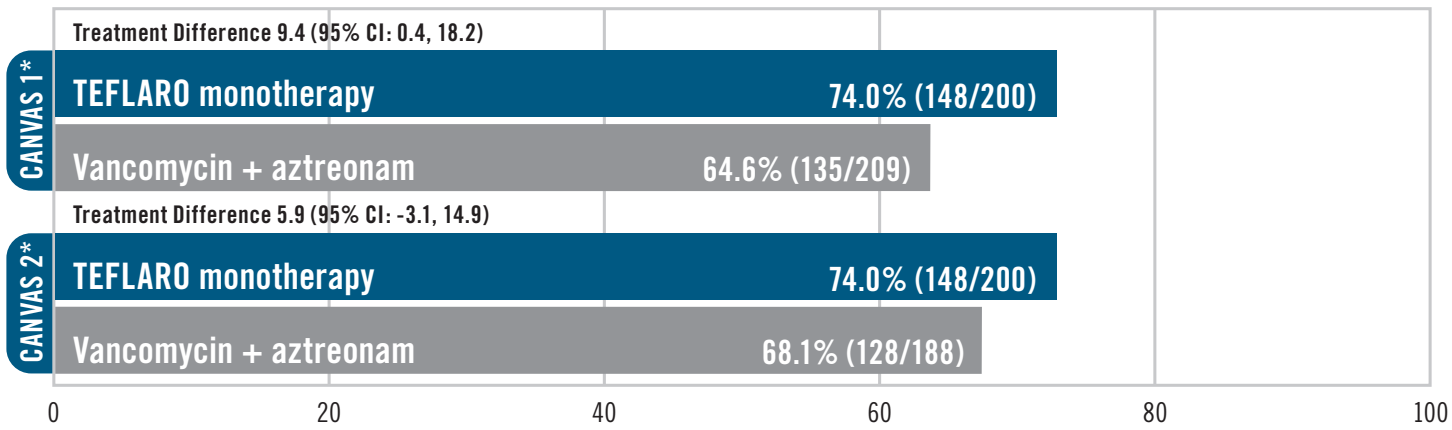
IMPORTANT SAFETY INFORMATION

Use in Specific Populations

- TEFLARO has not been studied in pregnant women. Therefore, TEFLARO should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.
- It is not known whether ceftaroline is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TEFLARO is administered to a nursing woman.
- Safety and effectiveness in pediatric patients have not been established.
- Because elderly patients, those ≥65 years of age, are more likely to have decreased renal function and ceftaroline is excreted primarily by the kidney, care should be taken in dose selection in this age group and it may be useful to monitor renal function. Dosage adjustment for elderly patients should therefore be based on renal function.
- Dosage adjustment is required in patients with moderate (CrCl >30 to ≤50 mL/min) or severe (CrCl ≥15 to ≤30 mL/min) renal impairment and in patients with end-stage renal disease (CrCl <15 mL/min).
- The pharmacokinetics of ceftaroline in patients with hepatic impairment have not been established.

ABSSSI

TEFLARO Demonstrated Clinical Response at Day 3 in Acute Bacterial Skin and Skin Structure Infections[1]

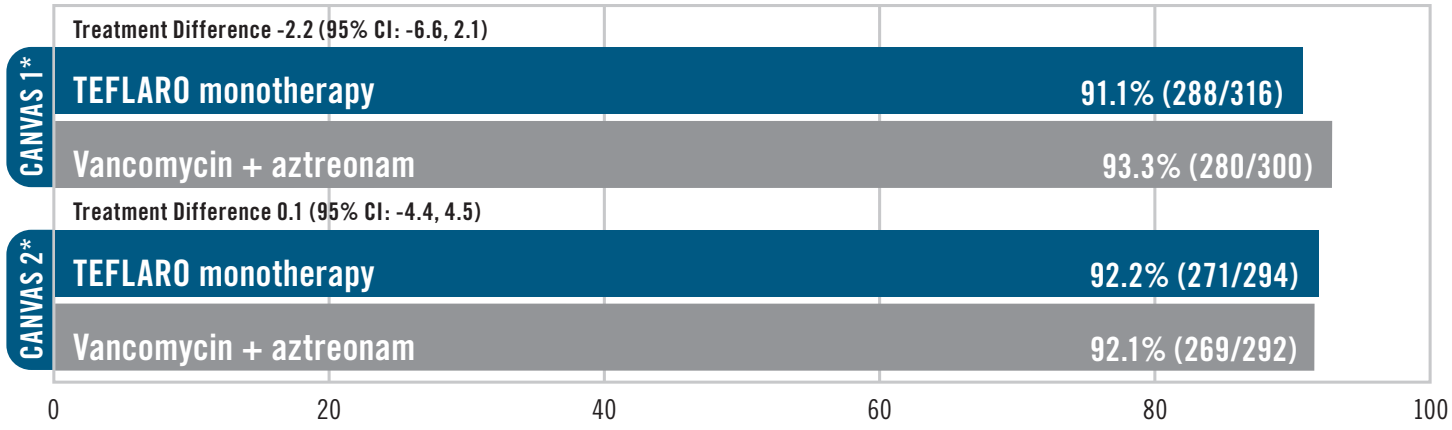


CI=confidence interval.

Neither trial established that TEFLARO was statistically superior to vancomycin plus aztreonam in terms of clinical response rates.

ABSSSI

TEFLARO Demonstrated Efficacy at TOC† (CE) in Acute Bacterial Skin and Skin Structure Infections[1]



CI=confidence interval.

Neither trial established that TEFLARO was statistically superior to vancomycin plus aztreonam in terms of clinical response rates.

*CANVAS=**C**eft**a**roli**n**e **v**s V**a**ncomycin in **S**kin and Skin Structure Infection. CANVAS 1=ABSSSI Trial 1, CANVAS 2=ABSSSI Trial 2.

†There are insufficient historical data to establish the magnitude of drug effect for antibacterial drugs compared with placebo at a TOC time point. Therefore, comparisons of TEFLARO to vancomycin plus aztreonam based on clinical response rates at TOC cannot be utilized to establish noninferiority.

References: 1. TEFLARO (ceftaroline fosamil) [prescribing information]. St Louis, MO: Forest Pharmaceuticals, Inc; 2011. **2.** Elixhauser A, Owens P. *Reasons for being admitted to the hospital through the emergency department, 2003*. Healthcare Cost and Utilization Project Statistical Brief #2. February 2006. Agency for Healthcare Research and Quality, Rockville, MD. www.hcup-us.ahrq.gov/reports/statbriefs/sb2.pdf. Accessed February 10, 2011. **3.** Data on file. Forest Laboratories, Inc.

Please see brief summary of Prescribing Information on following page.
Please also see full Prescribing Information at www.TEFLARO.com.

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OneBreath™ Family Activities Toolkit

OneBreath™: Make The Most Of It (onebreath.org) is an initiative of The CHEST Foundation, the philanthropic arm of the American College of Chest Physicians (ACCP).

Using the expertise of ACCP members who specialize in the prevention and treatment of diseases of the chest, OneBreath presents this information in accessible prevention tools, tips, and community-based activities as a benefit to ACCP members, their patients, and the community.

The newly developed "OneBreath Family Activities Toolkit" is for ACCP members, Ambassadors Group members, and other interested parties who wish to teach lung and heart health programs to children and families in their local areas by engaging them in fun, interactive educational programming.

The activity toolkit is derived from OneBreath's nine prevention strategies. It provides resources, ideas, helpful tips, and suggestions on how to develop and present cost-effective family events and activities focused on teaching prevention and encouraging healthy behaviors. The activities promote family learning and interactions that support the whole child and inspire a healthy outlook for all involved.

These family activities can be integrated into existing health and wellness events and programs at local children's hospitals, children's museums, and other community-based organizations that serve families.

The kit can also be disseminated in a train-the-trainer format for use by other organizations that work directly with children and families.

The OneBreath campaign emphasizes that living well means breathing well. With the generous support of donors and OneBreath online community members, OneBreath will serve as an inspiration for everyone, young and old, to take care of their lungs and heart and to never take their next breath for granted! ■

To access the full OneBreath Family Activities Toolkit, go to OneBreath.org.

Deadline for 2012 Medicare Payments

Beginning in 2012, there will be a penalty for Medicare providers who are not participating in the Electronic Prescribing (eRx) Incentive Program.

The penalty will be a reduction in Physician Fee Schedule payments by 1.0% in 2012, 1.5% in 2013, and 2% in 2014.

In order to avoid a penalty in 2012, an eligible physician or group practice must have documented 10 unique eRx events between the beginning of the year and June 30, 2011. ■

To read the full article, go to http://accpstorage.org/physician/2011/0311.pdf (go to page 20).

PCCSU Lessons for June

PCCSU
PULMONARY, CRITICAL CARE, SLEEP UPDATE

FROM THE CEO

Exceptional Leadership

Exceptional leadership doesn't just happen. For organizations like the ACCP, it results from concerted and sustained efforts to cultivate and recruit the right volunteers to meet identified needs. Even then, the College must regularly educate and assess its leadership to continue to flourish. As the current leader of the Board Governance Work Group of the American Society of Association Executives (ASAE) Executive Management Section Council, I emphasize to ASAE members the importance of seizing every opportunity to develop association leaders, beginning with Board meetings.

BY PAUL A. MARKOWSKI, CAE

At its meeting in March 2011, we asked the ACCP Board of Regents (Board) to consider what should be the top ACCP priorities for the next 3 years. Board members offered a wide range of goals, with a few overarching themes. Improving our technology infrastructure was stressed as key to moving the College forward in all areas. Sound financial planning, along with identifying new and alternative revenue sources, appeared on most priority lists.

Board members also stressed the importance of new partnerships with health-care and other societies and reaching out to the public through The CHEST Foundation's OneBreath™ campaign. Expanding and diversifying existing programs, such as AQuIRE and simulation, and developing education products were offered as high strategic concerns, as was ensuring that our leadership structure is best positioned to advance ACCP goals.

The Board summarized its leading priorities for the College to include:

- Continuing efforts to implement a new association management system for the ACCP.
- Maintaining a strong, diverse financial base to support our efforts.
- Maintaining and diversifying our successful programs.
- Growing our membership in many different ways, such as international, fellows, nonphysician providers, and others.
- Increased public awareness/branding of the College.
- Ensuring that our leadership structure is strategically aligned to advance ACCP priorities.

These ideas will be incorporated into the *ACCP Strategic Plan 2011-2012* for Board approval this month.

An important part of the role of Board members is to periodically assess their structure and work. Accordingly, we initiated a new Board self-assessment survey on the heels of the spring Board meeting. The survey covered a wide range of governance topics, including Board membership, policy, meetings, and fiscal monitoring; strategic planning; Board/CEO/staff relationship; and councils, committees, and task forces. The Board will discuss the survey results and identify steps toward increased effectiveness at its June meeting.

Our President-Elect, Dr. Suhail Raoof, FCCP, also identified leadership development as a central theme of his upcoming presidency and, in preparation for this, the Board will consider convening a leadership development task force this month.

The member and staff task force, spearheaded by Dr. Raoof, would develop a framework to (1) foster exceptional leadership for the College; (2) educate the general membership regarding effective leadership; and (3) increase opportunities for meaningful member engagement.

The framework would address leadership development of the Board, broader leadership, and general membership. For example, the task force might consider:

- Targeted and regular training for the Board, including orientation for new Board members.
- Leadership development as part of the opening session of the spring governance meeting and throughout the course of the year for ACCP leaders.
- A strategic leadership program for CHEST attendees.

The *ACCP Strategic Plan 2011-2012,* Board self-assessment, and ongoing Board focus on and discussion of those practices that contribute to exceptional leadership will, undoubtedly, culminate in new leadership development opportunities at the College. I encourage—as a volunteer-driven organization, we need—your active participation in these initiatives and in leading the ACCP toward its propitious future.

In a speech prepared for delivery in Dallas the day of his assassination, John F. Kennedy observed that "Leadership and learning are indispensable to each other." Exceptional learning is a prerequisite for exceptional leadership. Likewise, exceptional learning can't take place without exceptional leaders to champion it. We're committed to implementing best practices in leadership development at the College and, in so doing, the ACCP will continue to be the global leader in clinical education for chest medicine. ■

Product of the Month

ACCP-SEEK™ App

Enhance your knowledge of chest medicine with case-based questions that test your recall, interpretation, and problem-solving skills related to chest medicine. Access the recent editions of the pulmonary, critical care, and sleep medicine ACCP-SEEK® books in one app for use on the iPhone®, iPad®, or iPod touch®.

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Go to http://www.chestnet.org/iSEEK. ■

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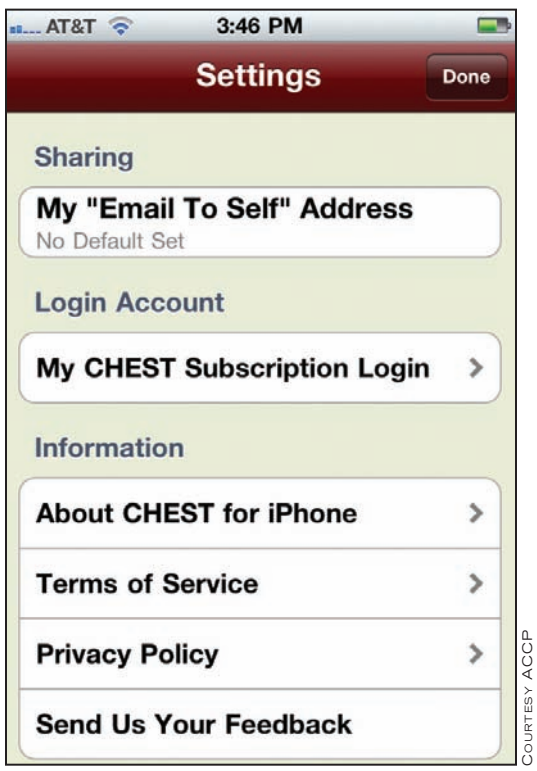
The series, so far, has touched on ventilator-associated tracheobronchitis, the dangers of water-pipe tobacco smoking, and the inaccuracy of Doppler echocardiography in pulmonary hypertension.

Stay tuned for more great conversations with moderator, Dr. D. Kyle Hogarth, FCCP, and contributing authors from *CHEST*. ■

CHEST Journal App Full-Text Articles Free Trial Ending

Although the trial period is ending in June, *CHEST* subscribers and members of the American College of Chest Physicians (ACCP) enjoy continuous access to *CHEST* full-text articles through the App by entering a subscriber user name and password just once.

- Launch the *CHEST* journal app.
- Click the gear icon (top right corner of iPhone or the top left corner on iPad "Current Issue" panel).
- Select "My *CHEST* Subscription Login."
- Enter your user name and password in the space provided, or use the help functions to retrieve your information.



COURTESY ACCP

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Other good news: The *CHEST* journal app for iPhone®, iPod touch®, and iPad® will remain free to download for all users, so don't hesitate to download your copy and take advantage of free access to tables of contents and complete abstracts.

Have another mobile device? Try the *CHEST* mobile site at m.chestjournal.chestpubs.org for a better search and browse experience. ■

NETWORKS
Nebulizers, CV Medicine, Infections, Pregnancy

Allied Health

A Revolution in Our Mi(d)st

Until recently, respiratory care practitioners (RCPs) were obliged to use "tee-type" nebulizers for bronchodilator aerosol treatments, over an industry-average treatment duration of 15 min. McPeck demonstrated that nine tee-type nebulizers delivered merely 7% to 15% of the dose ("charge") instilled into them (McPeck et al. *Respir Care.* 2004;49[11]:1393). Now, however, a new type of device—the "waste-reducing nebulizer"—is available. Monaghan's Aeroeclipse II™ is a breath-actuated nebulizer ("BAN"), while Westmed's Circulaire II™ and Healthline Medical's Medicator™ reduce waste by diverting medicated mist, which would otherwise be expelled into the bedside environment, into a "conserver" element and delivering it during the subsequent inspiration. McPeck empirically verified that BAN and conserver nebulizers deliver 33% and 34% of their charge, respectively, within a shorter treatment duration: 12 and 6 min, respectively. If a respiratory care department was to swap a BAN for a conventional nebulizer that exhibits an efficiency of 15%, productivity would be ([33/15] × [15/12] =) 275% of baseline for this task. If that department was currently employing a tee-type nebulizer, displaying a 7% efficiency, switching to the conserver type would result in an enormous productivity gain: ([34/7] × [15/6] =) 1,214%! On average, then, substitution of a waste-reducing nebulizer for a conventional nebulizer will elicit a whopping *sevenfold* increase in productivity, and patients will benefit by receiving more drug, and receiving it faster! Navigate to http://web.me.com/bobdemers/DCS_Website/Waste-Reducing-Nebulizers.html to see detailed results of our performance evaluation of waste-reducing nebulizers.

Bob Demers, RRT, NetWork Vice-Chair
Dr. Peter M. Browne, FCCP
Manny Banderas, RRT, MBA
Methodist Hospital of Southern California
Arcadia, CA

Cardiovascular Medicine and Surgery

RE-LY Trial

Dabigatran is an anticoagulant of the direct thrombin inhibitors class that offers an alternative to warfarin as the preferred orally administered anticoagulant, since it does not require blood tests for INR monitoring. It is approved by US Food and Drug Administration and indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. The RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy) trial evaluated the efficacy and safety of two different doses of dabigatran relative to warfarin in 18,113 patients with nonvalvular atrial fibrillation randomized to one of three arms: adjusted-dose warfarin; dabigatran, 110 mg bid; or dabigatran, 150 mg bid. Dabigatran 110 mg was noninferior to warfarin for the primary efficacy endpoint of stroke or systemic embolization (HR .90 , P = NS), while dabigatran 150 mg was significantly more effective than warfarin (HR .65; P = .001) or dabigatran 110 mg (HR .72, P = .004). Major bleeding was significantly less with dabigatran 110 mg than warfarin (2.71% vs 3.36%); dabigatran 150 mg showed similar bleeding to warfarin (3.11% vs 3.36%) (Connolly et al. *N Engl J Medicine.* 2009;361[12]:1139). GI bleeding was slightly higher with 150 mg bid vs warfarin (1.6% vs 1.1%). Dose should be reduced if the creatinine clearance value is less than 30 mL/min. It is contraindicated in patients with active bleeding, history of hypersensitivity reaction, or concomitant use with P-glycoprotein inducers (eg, rifampin).

Dr. Krishnaswami Vijayaraghavan, FCCP
Steering Committee Member

Chest Infections

IFN-γ Release Assays to Screen Health-care Workers for Mycobacterium tuberculosis *Infection: A Concise Update*

TB is a global threat to mankind. Globally, 9 million persons develop active disease attributable to *M tuberculosis* infection (MTBI) annually. Health-care workers (HCWs) are at increased risk of becoming infected with *M tuberculosis* through occupational exposure. Periodic screening of health-care workers for MTBI with tuberculin skin test (TST) is a common practice of many hospital infection control programs in the United States (*MMWR Recomm Rep.* 2005;54[RR17]:1). Interferon gamma (IFN-γ) release assays (IGRAs) are in vitro tests for MTBI that can be used in place of TST to screen health-care workers. Three IGRAs are commercially available for the detection of MTBI in the United States, including the QuantiFERON®-TB Gold In-Tube test (QFT-GIT; Cellestis Ltd; Valencia, CA). However, data on performance of QFT-GIT in such screening programs for health-care workers in the United States are limited. The study presented at CHEST 2010 (Joshi et al. *Chest.* 2010; 138:746A) pointed out the limitations of QFT-GIT, including the high number of positive test results despite negative TST history and high reversion rates (40%) on repeat testing that led to a dilemma in clinical decision making to offer MTBI treatment. Subsequently, another study (Gandra et al. *Infect Control Hosp Epidemiol.* 2010;31[12]:1279) and a meta-analysis (Zwerling et al. *Thorax.* Published online ahead of print, Jan 12, 2011) have raised similar concerns and proposed caution to interpret positive test results. These large studies in the real world will help guide many health-care institutions that are in the process of implementing IGRAs to replace TST. To conclude, QFT-GIT is not yet completely ready for prime time to replace the TST, and there is a major clinical learning curve ahead to fully understand the QFT-GIT test characteristics in low TB prevalence populations that undergo periodic screening.

Dr. Manish Joshi, FCCP
Steering Committee Member

Clinical Pulmonary Medicine

Pregnancy and the Lung

Pregnant women are prone not only to common pulmonary diseases but also diseases specific to pregnancy, eg, tocolysis-induced pulmonary edema, amniotic fluid embolism, and gestational trophoblastic neoplasms. Carrying a developing fetus poses additional challenges and restricts pharmacologic considerations.

In pregnancy, hyperventilation and respiratory alkalosis occur due to enhanced central sensitivity to CO_2, independent of progesterone levels (García-Rio et al. *Chest.* 1996;110[2]:446; Cugell et al. *Am Rev Tuberc.* 1953;67[5]: 568). $PaCO_2$ for a ventilated pregnant woman should be targeted 30-32 mm Hg (normal range), and marked respiratory alkalosis should be avoided as it decreases uterine blood flow. Maternal permissive hypercapnia is also deleterious because of fetal respiratory acidosis. The upper airway may be narrowed as pregnancy progresses due to edema and weight gain (Izci et al. *Eur Respir J.* 2006;27[2]:321), and endotracheal intubation can be difficult (Munnur et al. *Crit Care Med.* 2005;33[10 suppl]:S259). Similarly, many pregnant women suffer from obstructive sleep apnea (OSA) and 16% snore (Facco et al. *Obstet Gynecol.* 2010: 115[1]:77). OSA can be safely treated with CPAP (Guilleminault et al. *Sleep Med.* 2004;5[1]:43).

Bronchial hyperresponsiveness to methacholine (BHR) peaks at the

Continued on following page

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second trimester and reverts after delivery (Kwon et al. *Am J Obstet Gynecol.* 2004;190[5]:1). Miscarriage, depression, and caesarean section are more frequent among pregnant women with severe asthma (Tata et al. *Am J Respir Crit Care Med.* 2007;175[10]:991). Although gestational exposure to beta-agonists and inhaled and oral corticosteroids does not lead to fetal anomalies (Tata et al. *Thorax.* 2008;63[11]:981), smoking should be discouraged as it worsens asthma and causes intrauterine fetal growth retardation and congenital malformations (Murphy et al. *Thorax.* 2010; 65[8]:739; Newman et al. *Chest.* 2010;137[3]:601). Pulmonary embolism remains the major cause of maternal mortality, and venous thromboembolism accounts for 1.3 events per 1,000 deliveries, which represents a 10-fold risk increment compared with age-matched nonpregnant women. Low-molecular-weight heparin is recommended for the remainder of pregnancy until 6 weeks postpartum and stopped for 24 h before elective induction of labor (Bates SM et al. *Chest.* 2008;133[6 suppl]:844S).

For more information, attend the Clinical Pulmonary Medicine NetWork Highlight, "Clinical Challenges During Pregnancy" at CHEST 2011, scheduled for October 24, 11:00 AM – 12:30 PM, Pregnancy and the Lung.

Dr. Kay-Choong See
Dr. Pyng Lee, FCCP, Steering Committee Member

Critical Care

Tell Us What Critical Care Issues Are Important to You

Would you like to have your voice heard on critical care issues that you would like the ACCP to address? Now is your opportunity!

The Critical Care NetWork has spent considerable time this year completing a systematic needs assessment of the ACCP membership. The goal of this needs assessment has been to focus the efforts of the Critical Care NetWork Steering Committee to develop outstanding, relevant educational offerings and practice materials that you want and need to advance your daily clinical practice.

Although critical care topics make up a significant section of the CHEST program, the breadth and rapidly changing nature of this field creates a significant challenge for us to ensure that these sessions meet all the major areas that are important to the ACCP membership. The Critical Care NetWork Steering Committee is working to revise the ACCP critical care curriculum. We plan to use this framework, along with your feedback, to set our agenda for critical care sessions at future CHEST meetings and companion materials that will be developed through NetWork steering committee activities.

To voice your opinions, simply enter the following address into your internet browser: https://www.surveymonkey.com/s/CRM9VQD.

The survey is divided into two parts. The first section will take less than 5 min. You will then be asked if you are willing to answer a few additional questions, which will provide you with the opportunity to prioritize a variety of subjects under each topic area. The second part of the survey will take approximately 15 minutes.

Thank you in advance for your time and support.

LTC Alexander Niven, MC, USA, FCCP
NetWork Chair

This Month in *CHEST:* Editor's Picks

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

▶ **Integration of Clinical and Hemodynamic Parameters in the Prediction of Long-term Survival in Patients With Pulmonary Arterial Hypertension.** *By Dr. G. C. Kane, FCCP, et al.*

▶ **Noninvasive Diagnosis of Pulmonary Embolism.** *By Dr. P-Y Salaun et al.*

▶ **Flexible Pressure Delivery Modification of Continuous Positive Airway Pressure for Obstructive Sleep Apnea Does Not Improve Compliance With Therapy: Systematic Review and Meta-analysis.** *By Dr. J. P. Bakker; and Dr. N. S. Marshall.*

POINT/COUNTERPOINT

▶ **Is Measuring Sputum Eosinophils Useful in the Management of Severe Asthma?**
Yes. *By Dr. F. E. Hargreave; and Dr. P. Nair.*
No, not for most patients. *By Dr. S. P. Peters, FCCP.*

Critical Care Commentary

Critical Care Leadership in the Greater New York Area: A New Approach to Regionalization

Background

As the United States' population ages and health-care technology prolongs life for increasingly sicker patients, the number of people treated in ICUs is growing. While the overall number of hospital beds is on the decline, critical care medicine beds are steadily increasing in number and represent about 15% of hospital beds in the country, as well as $82 billion annually of total hospital costs (Halpern and Pastores. *Crit Care Med*. 2010;38[1]:65).

Growing costs and complexity of critical care in an environment of diminishing health-care resources magnify the need to streamline care delivery and education related to critical care services. Regionalization—in which health-care resources are distributed geographically in a tiered system with referral centers—has been offered as a potential strategy to streamline and improve critical care (Thompson et al. *Crit Care Med*. 1994;22[8]:1306; Singh and MacDonald. *Crit Care*. 2009;13[4]:219). This approach requires planning, geographic organization of beds, and regulatory oversight so that patients are treated in the most appropriate setting.

In the New York metropolitan region, critical care leaders are testing an alternative approach to regionalization: clinical leaders in the region work collaboratively to drive standardization, share training resources, and measure outcomes. With operational support and facilitation from the Greater New York Hospital Association (GNYHA) and the United Hospital Fund (UHF), the Critical Care Leadership Network (CCLN) has convened critical care professionals to establish new evidence-based health-care processes for ICU care to improve outcomes, lower costs, increase care coordination, and enhance communication within all hospital areas and departments.

In 2006, the GNYHA partnered with UHF to establish the CCLN to "regionalize" the critical care services using a collaborative structure that coordinates efforts across participating hospitals. The CCLN effort differs from traditional "regionalization of health-care services," where critical care medicine services are grouped together, redistributed, and sometimes eliminated. Instead, the GNYHA/UHF effort is driven by critical care clinicians practicing in the region who focus on continuous improvement, delineation of appropriate care delivery processes and methods to standardize and institute them, and innovative educational programming.

The CCLN comprises executive leadership and interdisciplinary hospital staff from GNYHA's member hospitals spanning New York, New Jersey, Connecticut, Rhode Island, and Pennsylvania. Participants are local and national leaders in the fields of critical care medicine, emergency medicine, and trauma, surgery, and nursing.

Patient Care Initiatives

The CCLN pursues its mission through the development and implementation of strategic programs and initiatives guided by its steering committee, composed of 31 physicians and nurses representing 20 GNYHA-member hospitals. This group sets overall regional priorities and designs and plans targeted activities in educational and patient care interventions using regional expertise and measuring clinical outcomes. The following efforts are completed or underway:

► *24-Hour ICU Survey.* In 2006, and again in 2007, the CCLN developed and administered a standard ICU survey tool to profile the region's critical care units over a single 24-h period. The survey was completed by 143 ICUs in 69 hospitals and captured de-identified data on 1,889 patients each year it was conducted. Data from the survey provided the CCLN and hospitals with insight into the areas of the ICU and hospital that need improvement, including information about resources and planning for surge capacity in emergencies, advance directives, patient throughput, and training and education needs.

► *Project Hypothermia.* The CCLN, along with medical staff from the Fire Department of New York City (FDNY), worked with directors of ICUs and EDs across New York City to develop a comprehensive, city-wide protocol for providing therapeutic hypothermia to eligible patients following cardiac arrest. The FDNY-launched NYC Project Hypothermia is entering a second phase in which Emergency Medical Services staff will induce hypothermia in the field. Participating hospitals submit data to FDNY to track the project's outcomes.

► *STOP Sepsis Collaborative.* In October 2010, the CCLN launched the Strengthening Treatment and Outcomes for Patients (*STOP*) Sepsis Collaborative to reduce mortality associated with severe sepsis and septic shock at 55 participating hospitals. A CCLN steering committee developed standardized processes for early identification and treatment of patients with severe sepsis and septic shock. The *STOP*-Sepsis Collaborative's 55 participating hospitals have approximately 22,000 acute care beds and more than 1 million annual discharges, making this initiative a significant opportunity to save lives, improve hospital processes and patient flow, and reduce costs associated with sepsis.

CCLN Training/Educational Programs

The CCLN offers extensive education programs to critical care clinicians that promote medical knowledge and procedural skills, while facilitating collaboration among critical care fellowship program directors in developing standardized curricula. All programs offered to date have been free for staff from GNYHA's nearly 150 member-hospitals. These programs included the following:

► *Critical Care Ultrasound Training.* The CCLN hosts an annual, intensive 3-day training program to teach first-year pulmonary and critical care fellows the use of ultrasonography in the care of critically ill patients. With hands-on training on volunteer subjects, participants develop skills in ultrasound imaging for vascular access; diagnosing lung, pleural, and abdominal disorders; and using basic echocardiography for critical care applications. Each volunteer faculty member works with only two fellows, and training is offered at no cost to participants. Faculty are on staff at GNYHA member hospitals, active in the CCLN, and many serve in national courses sponsored by the American College of Chest Physicians. A goal of the program is to create a cadre of fellows who go on to practice their skills throughout their careers and to pass on their expertise to their peers and, later, to their own trainees. Nearly 170 first-year fellows have participated to date. A comprehensive evaluation is carried out immediately after the program, along with ongoing follow-up to assess how the participants improved their skills and applied them to clinical practice.

► *Postoperative Care of the Cardiac Surgical Patient.* For the past 3 years, the CCLN hosted an annual daylong educational program for ICU staff, fellows, and referring physicians on caring for cardiac surgery patients in the ICU.

► *Emergency Preparedness.* The CCLN is involved in regional planning for catastrophic events, such as pandemic influenza or mass casualty. The CCLN also works with local agencies to determine the surge capabilities of hospital ICUs during various types of emergencies. Most recently, the CCLN participated in a program to train critical care clinicians to respond to major explosive events. As part of this initiative, the CCLN will also identify when and how to deliver critical care services outside the ICU.

► *End-of-Life and Palliative Care in the ICU.* The CCLN held a daylong educational program focused on addressing palliative and end-of-life care in the ICU. Regional experts shared their palliative care models and conducted a hands-on training workshop using real-life scenarios to improve communication skills and approach difficult decisions with families of critically ill patients.

► *Annual Symposium on Critical Care Controversies.* The CCLN hosts a daylong pro-con program on controversial issues in critical care, featuring experts from the New York region. Speakers examine the evidence behind practice recommendations, clinical guidelines, and ICU operations in a lively, debate-style format to encourage thoughtful discussion among the region's critical care providers.

Looking to the Future

The CCLN has firmly established itself as a resource for critical care professionals to improve patient care in the greater New York area. Participants in the CCLN's activities report enhanced improvement activities in their own institutions, greater collaboration within their hospitals and across departments, and increased collaboration and networking across the region on research, education, quality improvement, and emergency preparedness efforts. As such, the CCLN will continue to develop and pursue opportunities to improve quality and efficiency in the ICU. Future efforts will address the use of health information technology in critical care, optimal ICU staffing, and organizational configurations. ■

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For further information on this position, please contact Kristy Bailey, Physician Recruiter at (571) 423-5651, by email at kristy.bailey@inova.org, or fax your CV to (571) 423-5657. All inquiries will be handled in strict confidence. Please feel free to visit our website at www.inova.org.

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The VAMC Huntington, WV, is seeking a full-time or part-time BC/BE Pulmonologist. Responsibilities include coverage of clinics, completion of inpatient consults and regular coverage of our 10-bed missed Surgical/Medical ICU. Further responsibilities include teaching in the Pulmonary Fellowship Program and the Internal Medicine Residency Program. Successful applicants will receive a faculty appointment with the Joan C. Edwards School of Medicine at Marshall University. Applicants must possess active, unrestricted license in any US state.

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To apply for this position or for additional information, please forward CV or contact:

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Make Time for Beach Time

When visiting Hawaii, beach time is a must. Boasting some of the world's most beautiful beaches, Hawaii can offer tranquil turquoise waters and towering palm trees or the rolling 30-foot waves of which surfers dream.

To make it easier for you to get to the beach, education sessions at CHEST 2011 will end by mid to late afternoon, so you have time to hit the sand and surf. The hard part might be deciding where to go. But, your ACCP colleagues who live in Hawaii have made that easier by sharing their favorites. As you're making plans for Hawaii, be sure to check out these suggestions. (All these beaches are on Oahu, which is the island where CHEST 2011 will be held.)

CHEST 2011
October 22 - 26
Honolulu, Hawaii

Favorite Beaches

- Ala Moana Beach
- Bellows Beach
- Hanauma Bay
- Kailua Beach
- Laniakea Beach
- Lanikai Beach
- Sandy Beach
- Sherwoods Beach
- Waikiki Beach

Dr. Christine Fukui recommends Ala Moana Beach because it's close to the convention center, protected, and good for swimming distances. Even if you're not a swimmer, you should still visit Ala Moana. Dr. John Beamis, FCCP, says he doesn't swim much but still enjoys the walk, sunsets, and Friday night fireworks at the Hilton. Laniakea Beach, nicknamed "Turtle Beach," is great for viewing turtles in water and on sand. Dr. Warren Tamamoto, FCCP, says, "Waikiki Beach has everything—sunshine, clear water, and gentle waves. Plus, the zoo is nearby and Kapiolani Park is a great place for picnics or outdoor sports."

Best Place to See Big Waves

- Pipeline (The Banzai Pipeline)
- Sunset Beach
- Waimea Bay

These beaches, with their impressive waves, are on the north shore of Oahu. Dr. Tomamoto cautions to watch for high-surf warnings and to stay out of the water if the surf is up. Dr. Beamis recommends taking a day trip to the north shore to see the waves and to have lunch at any of the roadside shrimp stands.

Best Place for a Surf Lesson

- Waikiki Beach

If seeing the big waves makes you want to get out there and ride, consider a surf lesson. The one and only response for where to get a good surf lesson was Waikiki Beach. The waves are small, and lessons are readily available at many of the hotels.

Best Place for Swimming or Snorkeling

- Ala Moana Beach
- Hanauma Bay
- Ko Olina Resort
- Shark's Cove

Dr. Tamamoto recommends Ko Olina Resort for its manmade lagoons, which are very safe for families, but he also says, "Go to Hanauma Bay at least once while on Oahu. It's the best place for swimming or snorkeling." In addition to swimming or snorkeling, Dr. Fukui suggests body surfing at Ala Moana, Bellows, Kailua, Lanikai, or Sherwoods Beaches.

Mahalo to the ACCP members who shared their favorite beaches: Drs. John Beamis, John Chen, Christine Fukui, Alvin Furuike, Don Helman, Sailaja Kolli, and Warren Tamamoto. If you see these members at CHEST 2011, be sure to tell them how you like their suggestions, and ask them for more!

Courtesy Tor Johnson/Hawaii Tourism Authority

Hawaii has many beautiful beaches you can visit during CHEST 2011.

CHEST 2011 is October 22 - 26 in Honolulu, Hawaii. Postgraduate multipass courses and additional courses will begin Saturday, October 22, and general sessions will begin Sunday, October 23. New this year, after-CHEST postgraduate courses will be held Friday, October 28, and Saturday, October 29, so you can continue your learning momentum and take in more of Hawaii. Learn more about CHEST 2011 at www.accpmeeting.org. ■

FROM THE DESK OF THE PRACTICE MANAGEMENT COMMITTEE

Accountable Care Organizations (ACOs)

BY DR. ROBERT DEMARCO, FCCP, CHAIR; AND DONNA KNAPP BYBEE, MA, FACMPE, VICE-CHAIR

On March 31, 2011, the Centers for Medicare & Medicaid Services (CMS) proposed new rules under the Affordable Care Act to govern how doctors, hospitals, and other providers coordinate care for Medicare patients through Accountable Care Organizations (ACOs). An ACO is a group of health-care providers working together to provide consistent, quality, and timely patient care to a group of patients.

Under the proposed rule, CMS would develop benchmarks for each ACO to determine whether it qualifies to receive shared savings or if it will be held accountable for losses. This rule would go into effect at the beginning of 2012. According to the Affordable Care Act, an ACO would manage all of the health-care needs for a minimum of 5,000 Medicare beneficiaries for a minimum of 3 years.

CMS is proposing to implement two separate risk models for ACOs to opt into, a one-sided risk model and a two-sided risk model. The one-sided risk model would have ACOs sharing only in savings for the first 2 years, then sharing in savings *and* losses in the third year. The two-sided risk model would have ACOs sharing in savings and losses for all 3 years.

CMS believes having two options would have the advantage of providing an entry point for ACOs with less experience with risk models to gain experience with population management before transitioning to a risk-based model, while also providing an opportunity for more experienced ACOs to enter an agreement to have access to a greater share of savings but also have the risk of repaying Medicare a portion of any expenditures over budget.

The CMS proposed rule estimates that 1.5 to 4 million Medicare patients will receive care from an ACO.

Payouts could reach $800 million in bonuses over the first 3 years; the CMS also estimates that it would levy $40 million in penalties in that same period.

Payment for ACOs is tied to quality metrics and reductions in total cost in care. The main goal of an ACO is to provide high-quality and seamless care for Medicare beneficiaries. The ACO model will not do away with fee for service; CMS would still pay individual providers who belong to an ACO for specific services or choose to remain independent and serve the Medicare population not covered under the ACO. ACO pilot projects are being conducted to study different reimbursement models.

The Medicare Shared Saving Program, which was created by the Affordable Care Act, will reward ACOs that lower growth in health-care costs while meeting performance quality metrics.

These metrics will fall into the following categories: patient experience, care coordination, patient safety, preventive health, and at-risk population/frail elderly health.

Provider participation in an ACO is voluntary. Practices must review their strategic plan, their community provider base, physician lifestyle issues, current and projected reimbursement patterns, and patient demographics to determine if they should join an ACO by becoming employees of a larger system; create an ACO; remain independent; or create another applicable model that complies with the goals of health-care reform.

Over the last several decades many strong forces have had a major impact on the health-care industry.

Regardless of what model physicians choose to serve their patients, it is vital to be part of the governance structure to ensure that they have a voice in their future and the future of their patients. ■

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*Reports were subjective and recorded in a daily diary form.[4]

References: 1. ZENPEP [package insert]. Yardley, PA: Eurand Pharmaceuticals, Inc.; 2010. **2.** Data on file MED-0151, Eurand Pharmaceuticals, Inc., Yardley, PA. **3.** Data on file MED-0152, Eurand Pharmaceuticals, Inc., Yardley, PA. **4.** Wooldridge JL, Heubi JE, Amaro-Galvez R, et al. EUR-1008 pancreatic enzyme replacement is safe and effective in patients with cystic fibrosis and pancreatic insufficiency. *J Cyst Fibros*. 2009;8(6):405-417.

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