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"The biggest need was to facilitate collaboration between multiple providers," Dr. Savithri Nageswaran said.

Pediatric Palliative Care Still Too Rare

BY CHRISTINE KILGORE

Elsevier Global Medical News

Dr. Stefan J. Friedrichsdorf has a list of "myths" about pediatric palliative care that he presents during lectures. Among them: that the death of a child in the United States is a rare event, that pediatric palliative care is just for children with cancer, and that care starts when treatment stops.

In his lectures – and in his work every day at Children's Hospitals and Clinics of Minnesota, Minneapolis – Dr. Friedrichsdorf debunks these myths.

In January, he was one of two pediatricians who won national awards from the Hastings Center and a partnering foundation for their contributions to the broader field of palliative care. He and pediatrician Dr. Savithri Nageswaran of Brenner Children's Hospital at Wake Forest University Baptist Medical Center in Winston-Salem, N.C., joined two geriatricians and an internist in receiving the award.

The pain and palliative care program at Dr. Friedrichsdorf's institution is a relatively long-standing program, but pediatric palliative care is a new subspecialty and is still a relatively new area of pediatric care and of palliative medicine – one for which delivery models and educational pathways are still evolving, and one for which reimbursement is poor and regulatory barriers are challenging.

"It's truly interdisciplinary, in that people need to really go beyond what they've been trained for," said Dr. Friedrichsdorf, who is medical director of the department of pain medicine, palliative care, and integrative medicine at Children's. "I'm nothing without my team."

Pediatric palliative care has been defined and described by the World Health Organization, the Institute of Medicine, the American Academy of Pediatrics, and other bodies as individualized, integrative care that is provided for children with life-threatening conditions.

See **Pediatric** • *page 23*

Bariatric Surgery Deaths Tied to Sleep Apnea

Screening for OSA should be standard.

BY M. ALEXANDER OTTO

Elsevier Global Medical News

HUNTINGTON BEACH, CALIF. – Underrecognized and undertreated obstructive sleep apnea is the most likely cause of unexplained deaths following bariatric surgery, according to results of a small pilot study.

Because of that, continuous positive airway pressure (CPAP) and continuous pulse oximetry monitoring – with alarms to alert nursing staff to hypoxic episodes and rouse oxygen-desaturated patients from sleep – should be included in postoperative care, said Dr. Scott Gallagher, a bariatric surgeon at the University of South Florida, Tampa, where the study was conducted.

In previous work, the researchers found that severe, prolonged, and frequent arterial hypoxemia is common in sleeping bariatric surgery patients. They sought to determine why such patients – who seemed to be doing well after surgery – died suddenly in their sleep, without pulmonary embolism or any other obvious cause. In 15 gastric bypass patients monitored for 24 hours after surgery, they found that the average episode of hypoxemia lasted 21 minutes, and the longest for hours. Blood oxygen saturation fell as low as 60% (J. Surg. Res. 2010;159:622-6).

Right-to-left shunt, diminished inspired oxygen partial pressure, and other textbook causes "didn't exist in these patients," Dr. Gallagher said.

That left either postoperative, narcotic-induced hypoventilation or obstructive sleep apnea as the most likely explanation. Narcotic pain control is common after bariatric surgery, as is sleep apnea.

See **Bariatric** • *page 20*

Once-Daily Drug on Horizon for COPD

BY ELIZABETH MECHCATIE

Elsevier Global Medical News

SILVER SPRING, MD. – The majority of a Food and Drug Administration advisory panel recommended that the inhaled bronchodilator indacaterol should be approved for patients with chronic obstructive pulmonary disease, to be taken at a dose of 75 mcg once daily.

Two weeks later, however, the FDA told the drug's maker, Novartis, that the agency would need 3 more months to complete the review of indacaterol's research data.

At an initial meeting in March, the FDA's Pulmonary-Allergy Drugs Advisory Committee voted 13-4 that the data on the safety and efficacy of the 75-mcg dose of indacaterol, as a maintenance treatment, provided substantial evidence to support the drug's approval at this dose, for the proposed indication: the long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic

See **Drug** • *page 2*

INSIDE

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FDA Considering LABA for COPD

Drug • *from page 1*

obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

The majority of the panel agreed that the 150-mcg once-daily dose had not been shown to be effective, largely because of the limited amount of data directly comparing the two doses.

Indacaterol, a long-acting beta$_2$ adrenergic agonist (LABA) that is administered in a dry-powder inhaler, has a rapid onset of effect sustained over 24 hours, according to Novartis, which filed for approval of two once-daily doses: 75 mcg and 150 mcg. But in a 12-5 vote, the panel recommended against approval of the higher dose, largely because of the paucity of data directly comparing the two doses and, as panel chair Dr. Peter Terry, FCCP, professor of medicine, Johns Hopkins University, Baltimore, said, "no compelling evidence that there was a significant difference" between the two doses.

The 150-mcg once-daily dose and a higher dose (300 mcg once daily) of indacaterol were approved to treat COPD in the European Union in September 2009, where it is marketed as the Onbrez Breezhaler; the drug at those doses is now approved in more than 50 countries.

Initially, Novartis had applied for approval of these two doses in December 2008, but the FDA requested that the company study lower doses of the drug, after the agency review concluded that no clinically meaningful advantage had been shown for the 300-mcg dose over the 150-mcg dose, and also because of safety concerns. There were more cardiovascular and cerebrovascular adverse events among patients with COPD treated with indacaterol, when compared with those on placebo and the active compactor, formoterol. In studies of indacaterol in patients with asthma, there were some deaths, possibly related to indacaterol, which raised concerns because treatment with inhaled LABAs as monotherapy has been associated with severe asthma exacerbations and asthma-related deaths, described in the boxed warning included in the prescribing information of these drugs. Although the mechanism has not been identified, data from controlled and epidemiologic studies suggest that higher doses may contribute to this increased risk, according to the FDA.

'A SUBSTANTIAL NUMBER OF PATIENTS WITH MODERATE TO SEVERE COPD ... WILL BENEFIT FROM THIS MEDICATION, WITHOUT SUBSTANTIAL RISKS.'

In response, the company conducted more studies and analyses, and submitted data on the 75-mcg and 150-mcg once-daily doses in about 2,700 patients with COPD, and proposed those two doses for approval, recommending the 150-mcg dose as the starting dose.

At the FDA meeting, Novartis presented the results of five phase III studies of the 75-mcg, 150-mcg, and 300-mcg doses, compared with placebo or active controls in approximately 4,000 mostly white patients with COPD, whose mean age was about 64 years. After 12 weeks, there were significant improvements in lung function, as measured by trough FEV_1 associated with each dose, when compared with placebo. In the safety database of patients with COPD, the risk of serious cardiovascular events (including MI, stroke, or cardiac death) was not increased, and there was no increase in acute respiratory events associated with any dose of indacaterol studied, according to Novartis.

FDA reviewers concluded that there was no clinically meaningful difference in efficacy between the 75-mcg dose and the two higher doses, raising the question of whether the higher dose was necessary. Most of the panelists agreed.

"I do believe that at this dose a substantial number of patients with moderate to severe COPD in the United States will benefit from this medication, without substantial risks," said one of the panelists, Daren Knoell, Pharm.D., professor of pharmacy and medicine at Ohio State University and the Davis Heart and Lung Institute, Columbus. He referred to "consistent" evidence across virtually all trials that the 75-mcg once-daily dose benefited most patients.

Novartis has proposed a risk evaluation and mitigation strategy (REMS) to manage the potential risks of the drug, which would include educating health care professionals about the appropriate indications for indacaterol and about the increased risk of asthma-related deaths associated in asthma patients treated with LABAs as monotherapy.

If both doses were approved, indacaterol would be the first bronchodilator in the United States to be approved at two doses for the treatment of COPD; currently, only one dose of formoterol and salmeterol, which are also LABAs, are approved for COPD treatment.

A final decision on approval is not expected until the summer. In a statement issued in late March, Novartis said that the FDA has asked for a 3-month extension of its review of indacaterol, which is expected to be completed by July.

If approved, the company plans to market indacaterol in the United States as the Arcapta Neohaler.

Novartis has conducted studies of the drug in patients with asthma, but is not filing for approval for an asthma indication in the United States or elsewhere. Some concern about off-label use of the product in patients with asthma was expressed at the meeting.

The FDA usually follows the recommendations of its advisory panels. Panel members have been cleared of potential conflicts of interest by the FDA prior to meetings; occasionally, the FDA grants a waiver to a panelist with a conflict, but this was not necessary at this meeting. ■

COMMENTARY

Dr. Darcy Marciniuk, FCCP, comments: The desire to have an effective once-a-day long-acting beta$_2$ agonist in our COPD tool kit may soon become a reality. The medication dosing needs to get sorted out – we'll be watching closely for the FDA opinion on this issue. The real benefit of this medication may be in future single-delivery system combinations with other effective inhaled COPD therapies.

IN THIS ISSUE

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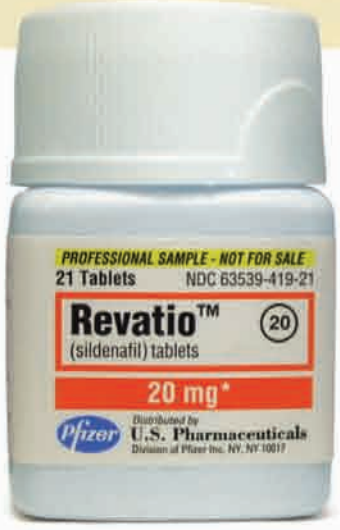

Indication

REVATIO is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability and delay clinical worsening. Delay in clinical worsening was demonstrated when REVATIO was added to background epoprostenol therapy. The efficacy of REVATIO has not been adequately evaluated in patients taking bosentan concurrently.

Important Safety Information

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

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

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

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

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

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

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

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

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

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

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

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

Revatio®
sildenafil
20 mg tablets
Start With Confidence™

Please see Brief Summary of Prescribing Information on the following pages.

www.REVATIO.com

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Ho'olu komo la kaua (Please Join Us) at CHEST 2011

The fresh, floral air will energize you. The warm, tranquil waters will refresh you. The breath-taking, natural beauty will renew you. Hawaii is like no other place on earth, and it's the destination for CHEST 2011, Oct 22-26, in Honolulu.

The unique Hawaiian setting will be complemented by an equally unique CHEST 2011 program, which is designed to allow you to take in Hawaii. CHEST 2011 and one of the three after-CHEST postgraduate courses will be on the "Big Island," while the other two after-CHEST postgraduate courses will be on Maui and Oahu, providing you an opportunity to visit neighboring islands. CHEST 2011 programs and sessions will start earlier in the morning and end by midafternoon, giving you time to enjoy the tropical setting. General sessions end Oct 26, and after-CHEST postgraduate courses begin Oct 28, leaving Thursday, Oct 27, as a day for you to spend as you wish.

The average year-round temperature is 77° F (or 25° C), so pack summer attire and a light jacket or sweater for the evenings. Suits and ties are very rarely worn in Hawaii. Bring casual dress clothes or resort wear if you plan on experiencing the nightlife.

Details about CHEST 2011 are available at accpmeeting.org. Click the "Destination + Travel" tab, where you can link to discounts for dining, attractions, and entertainment and watch a short video about Hawaii. Also, check out chest2011.hawaiiconvention.com, a CHEST 2011 microsite developed by the Hawaiian Convention Bureau. Use the language selector in the upper right corner to choose English, Japanese, Korean, or Simplified or Traditional Chinese. ■

REVATIO® (SILDENAFIL)

Brief Summary of Prescribing Information

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

Limitation of Use

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

DOSAGE AND ADMINISTRATION

Pulmonary Arterial Hypertension (PAH)

REVATIO Tablets

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

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

REVATIO Injection

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

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

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

CONTRAINDICATIONS

Use with Organic Nitrates

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

Hypersensitivity Reactions

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

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

WARNINGS AND PRECAUTIONS

Cardiovascular Effects

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

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

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

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

Use with Alpha-blockers

PDE5 inhibitors, including sildenafil, and alpha-adrenergic blocking agents are both vasodilators with blood pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes can lower blood pressure significantly, leading to symptomatic hypotension. In the sildenafil interaction studies with alpha-blockers, cases of symptomatic hypotension consisting of dizziness and lightheadedness were reported *[see Drug Interactions]*. No cases of syncope or fainting were reported during these interaction studies. The safety of combined use of PDE5 inhibitors and alpha-blockers may be affected by other variables, including intravascular volume depletion and concomitant use of anti-hypertensive drugs.

Effects on Bleeding

In humans, sildenafil has no effect on bleeding time when taken alone or with aspirin. In vitro studies with human platelets indicate that sildenafil potentiates the anti-aggregatory effect of sodium nitroprusside (a nitric oxide donor). The combination of heparin and sildenafil had an additive effect on bleeding time in the anesthetized rabbit, but this interaction has not been studied in humans.

The incidence of epistaxis was 13% in patients taking sildenafil with PAH secondary to connective tissue disease (CTD). This effect was not seen in primary pulmonary hypertension (PPH) (sildenafil 3%, placebo 2%) patients. The incidence of epistaxis was also higher in sildenafil-treated patients with a concomitant oral vitamin K antagonist (9% versus 2% in those not treated with concomitant vitamin K antagonist).

The safety of REVATIO is unknown in patients with bleeding disorders or active peptic ulceration.

Use with Ritonavir and Other Potent CYP3A Inhibitors

The concomitant administration of the protease inhibitor ritonavir (a highly potent CYP3A inhibitor) substantially increases serum concentrations of sildenafil; therefore, co-administration of ritonavir or other potent CYP3A inhibitors with REVATIO is not recommended.

Effects on the Eye

Advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking PDE5 inhibitors, including REVATIO. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, that has been reported postmarketing in temporal association with the use of all PDE5 inhibitors, including sildenafil, when used in the treatment of erectile dysfunction. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should also discuss the increased risk of NAION with patients who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE5 inhibitors *[see Adverse Reactions]*.

There are no controlled clinical data on the safety or efficacy of REVATIO in patients with retinitis pigmentosa, a minority whom have genetic disorders of retinal phosphodiesterases. Prescribe REVATIO with caution in these patients.

Hearing Impairment

Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE5 inhibitors, including REVATIO. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to 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 *[see Adverse Reactions]*.

Combination with other PDE5 inhibitors

Sildenafil is also marketed as VIAGRA®. The safety and efficacy of combinations of REVATIO with VIAGRA or other PDE5 inhibitors have not been studied. Inform patients taking REVATIO not to take VIAGRA or other PDE5 inhibitors.

Prolonged Erection

Use REVATIO with caution in patients with anatomical deformation of the penis (e.g., angulation, cavernosal fibrosis, or Peyronie's disease) or in patients who have conditions, which may predispose them to priapism (e.g., sickle cell anemia, multiple myeloma, or leukemia). In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism (painful erection greater than 6 hours in duration) is not treated immediately, penile tissue damage and permanent loss of potency could result.

ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Hypotension *[see Warnings and Precautions]*
- Vision loss *[see Warnings and Precautions]*
- Hearing loss *[see Warnings and Precautions]*
- Priapism *[see Warnings and Precautions]*

Clinical Trials Experience

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.

Safety data were obtained from the 12 week, placebo-controlled clinical study and an open-label extension study in 277 treated patients with pulmonary arterial hypertension.

Doses up to 80 mg TID were studied.

The overall frequency of discontinuation in REVATIO-treated patients at the recommended dose of 20 mg TID was 3% and was the same for the placebo group.

In the placebo-controlled trial in pulmonary arterial hypertension, the adverse drug reactions that were reported by at least 3% of REVATIO patients treated at the recommended dosage (20 mg TID) and were more frequent in REVATIO patients than placebo patients, are shown in Table 1. Adverse events were generally transient and mild to moderate in nature.

Table 1. REVATIO All Causality Adverse Events in ≥ 3% of Patients and More Frequent (> 1%) than Placebo

ADVERSE EVENTS %	Placebo (n=70)	Revatio 20 mg TID (n=69)	Placebo-Subtracted
Epistaxis	1	9	8
Headache	39	46	7
Dyspepsia	7	13	6
Flushing	4	10	6
Insomnia	1	7	6
Erythema	1	6	5
Dyspnea exacerbated	3	7	4
Rhinitis nos	0	4	4
Diarrhea nos	6	9	3
Myalgia	4	7	3
Pyrexia	3	6	3
Gastritis nos	0	3	3
Sinusitis	0	3	3
Paresthesia	0	3	3

nos: Not otherwise specified

At doses higher than the recommended 20 mg TID, there was a greater incidence of some adverse events including flushing, diarrhea, myalgia and visual disturbances. Visual disturbances were identified as mild and transient, and were predominately colortinge to vision, but also increased sensitivity to light or blurred vision.

The incidence of retinal hemorrhage at the recommended sildenafil 20 mg TID dose was 1.4% versus 0% placebo and for all sildenafil doses studied was 1.9% versus 0% placebo. The incidence of eye hemorrhage at both the recommended dose and at all doses studied was 1.4% for sildenafil versus 1.4% for placebo. The patients experiencing these events had risk factors for hemorrhage including concurrent anticoagulant therapy.

PAUL A. MARKOWSKI, CAE

FROM THE CEO

Diversity and Inclusivity

At CHEST 2010 held in Vancouver, I announced the creation of a Presidential Task Force on Diversity. The Task Force on Diversity has been meeting and working hard to provide the ACCP with recommendations to ensure optimal integration of diversity and inclusivity (D&I) throughout the activities and structure of the College.

The task force has committed and dedicated members who we are proud to have and who should receive our thanks in advance for taking on this very important initiative.

While it is important to have created and engaged this task force, its members cannot do this alone. This initiative needs champions at all levels, including at the top of the ACCP. We have that enthusiastic spirit within the ACCP leadership, and I'm here to tell you that you have it in me, your EVP and CEO.

I decided this initiative needed to be added to my plate of strategic activities. I have recently participated in one of the top conferences in the professional association world and have come away with one of the most profound learning experiences of my career.

Working with the Institute for Nonprofit Research, Education, and Engagement at North Carolina State University, the American Society of Association Executives (ASAE) commissioned research resulting in a white paper on "Enhancing Diversity and Inclusion in Membership Associations" (www.asaecenter.org/foundation2/documents/ncsudivincreport.pdf). This research paper was the basis for the conference I attended.

It was determined that diversity can lead to better organizational performance but only if it is effectively managed. Associations with strong D&I emphasis and priorities are characterized as having a high level of comfort with conflict and change. They are associations that empower others and take a long-term view. They are associations that consider costs and benefits to the participants and have institutionalized policies and practices. There is no one-size-fits-all approach. Associations must carefully determine the specific approach that will work for their organization. Finally, strong associations see D&I as aligned with their mission and values.

So, how does the ACCP measure up to the characteristics identified above? Where would we be ranked in comparison with the other organizations with which you may personally be involved? I know as I have looked over the past 24 years of my association career, I can see room for improvement at the ACCP. Yet, we should not see ourselves as behind, because, in fact, we are very comparable to many other associations. But, is that where we want to be? The ACCP is the leader in many areas. Why not be the leader in D&I?

So, I would like to ask every one of you to be a champion for D&I at the ACCP. We need everyone to embrace this initiative. It is not only good for the ACCP as an association and business, it is good for you as the caring practitioner you are for your patients. ■

In a placebo-controlled fixed dose titration study of REVATIO (starting with recommended dose of 20 mg TID and increased to 40 mg TID and then 80 mg TID) as an adjunct to intravenous epoprostenol in pulmonary arterial hypertension, the adverse events that were reported were more frequent than in the placebo arm (>6% difference) are shown in Table 2.

Table 2. REVATIO-Epoprostenol Adverse Events More Frequent (> 6%) than Placebo

ADVERSE EVENTS %	Placebo Epoprostenol (n = 131)	Revatio Epoprostenol (n = 134)	Placebo-Subtracted %
Headache	34	57	23
Edema^	13	25	14
Dyspepsia	2	16	14
Pain in extremity	6	17	11
Diarrhea	18	25	7
Nausea	18	25	7
Nasal congestion	2	9	7

^includes peripheral edema

REVATIO Injection

REVATIO injection was studied in a 66-patient, placebo-controlled study at doses targeting plasma concentrations between 10 and 500 ng/mL (up to 8 times the exposure of the recommended dose). Adverse events in PAH patients were similar to those seen with oral tablets.

Postmarketing Experience

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

Cardiovascular Events

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

Decreases in and Loss of Vision

When used to treat erectile dysfunction, non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported postmarketing in temporal association with the use of phosphodiesterase type 5 (PDE5) inhibitors, including sildenafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors *[see Warnings and Precautions]*.

Loss of Hearing

Cases of sudden decrease or loss of hearing have been reported postmarketing in temporal association with the use of PDE5 inhibitors, including REVATIO. In some of the cases, medical conditions and other factors were reported that may have also played a role in the otologic adverse events. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of REVATIO, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors *[see Warnings and Precautions]*.

Other Events

The following list includes other adverse events that have been identified during postmarketing use of REVATIO. The list does not include adverse events that are reported from clinical trials and that are listed elsewhere in this section. These events have been chosen for inclusion either due to their seriousness, reporting frequency, lack of clear alternative causation, or a combination of these factors. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Nervous system: Seizure, seizure recurrence

DRUG INTERACTIONS

Nitrates

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

Ritonavir and other Potent CYP3A Inhibitors

Concomitant use of REVATIO with ritonavir and other potent CYP3A inhibitors is not recommended *[see Warnings and Precautions]*.

Alpha-blockers

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

In drug-drug interaction studies, sildenafil (25 mg, 50 mg, or 100 mg) and the alpha-blocker doxazosin (4 mg or 8 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on doxazosin therapy. In these study populations, mean additional reductions of supine systolic and diastolic blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, respectively, were observed. Mean additional reductions of standing blood pressure of 6/6 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively, were also observed. There were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and light-headedness, but not syncope.

Amlodipine

When sildenafil 100 mg oral was co-administered with amlodipine, 5 mg or 10 mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was 8 mmHg systolic and 7 mmHg diastolic.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

No evidence of teratogenicity, embryotoxicity, or fetotoxicity was observed in pregnant rats or rabbits dosed with sildenafil 200 mg/kg/day during organogenesis, a level that is, on a mg/m^2 basis, 32- and 68-times, respectively, the recommended human dose (RHD) of 20 mg TID. In a rat pre- and postnatal development study, the no-observed-adverse-effect dose was 30 mg/kg/day (equivalent to 5-times the RHD on a mg/m^2 basis). There are, however, no adequate and well-controlled studies of sildenafil in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

The safety and efficacy of REVATIO during labor and delivery has not been studied.

Nursing Mothers

It is not known if sildenafil or its metabolites are excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when REVATIO is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of sildenafil in pediatric pulmonary hypertension patients have not been established.

Geriatric Use

Clinical studies of REVATIO did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Hepatic Impairment

No dose adjustment for mild to moderate impairment is required. Severe impairment has not been studied.

Renal Impairment

No dose adjustment is required (including severe impairment CLcr < 30 mL/min).

OVERDOSAGE

In studies with healthy volunteers of single doses up to 800 mg, adverse events were similar to those seen at lower doses but rates and severities were increased.

In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and it is not eliminated in the urine.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Sildenafil was not carcinogenic when administered to rats for up to 24 months at 60 mg/kg/day, a dose resulting in total systemic exposure (AUC) to unbound sildenafil and its major metabolite 33 and 37 times, for male and female rats respectively, the human exposure at the RHD of 20 mg TID. Sildenafil was not carcinogenic when administered to male and female mice for up to 21 and 18 months, respectively, at doses up to a maximally tolerated level of 10 mg/kg/day, a dose equivalent to the RHD on a mg/m^2 basis.

Sildenafil was negative in *in vitro* bacterial and Chinese hamster ovary cell assays to detect mutagenicity, and *in vitro* human lymphocytes and *in vivo* mouse micronucleus assays to detect clastogenicity.

There was no impairment of fertility in male or female rats given up to 60 mg sildenafil/kg/day, a dose producing a total systemic exposure (AUC) to unbound sildenafil and its major metabolite of 19 and 38 times for males and females, respectively, the human exposure at the RHD of 20 mg TID.

PATIENT COUNSELING INFORMATION

- Inform patients of contraindication of REVATIO with regular and/or intermittent use of organic nitrates.
- Inform patients that sildenafil is also marketed as VIAGRA for erectile dysfunction. Advise patients taking REVATIO not to take VIAGRA or other PDE5 inhibitors.
- Advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking REVATIO. Such an event may be a sign of NAION.
- Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking REVATIO. These events may be accompanied by tinnitus and dizziness.

RX only

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PCCSU Lessons for April

► *Update on the Evaluation of Intravascular Fluid Status in Critically Ill Patients.* By Dr. Sumit Singh and Dr. Geoffrey K. Lighthall.

► *The Value of Bronchoalveolar Lavage in the Diagnosis and Management of Interstitial Lung Disease.* By Dr. Keith C. Meyer, FCCP.

PCCSU
PULMONARY, CRITICAL CARE, SLEEP UPDATE

PQRS Incentive Program and Noncompliance Penalty

BY DIANE KRIER-MORROW, MBA, MPH, CCS-P; AND MARLA BRICHTA

The Physician Quality Reporting System (PQRS), formerly known as the Physician Quality Reporting Initiative (PQRI), is a Medicare reporting program that offers an incentive payment to physicians (and other eligible professionals) who satisfactorily report data on quality measures during a specified reporting period. PQRS reporting is voluntary for 2011-2014, though practices not participating are missing available incentive payments. A penalty for not participating in PQRS will begin in 2015, with a proposed 1.5% reduction in all Medicare fee-for-service payments and a reduction of 2.0% in 2016. The penalty for noncompliance will also continue beyond 2016.

The base incentive payment for 2011 is 1% Medicare Part B physician fee-for-service (PFS) allowed charges for all covered professional services (0.5% for each year, 2012-2014). An additional incentive payment of 0.5% for participating in the new Maintenance of Certification Program (MOCP) is available for 2011-2014.

To qualify for the PQRS incentive, the correct numerator Quality-Data Code must be reported on at least 50% of the claims eligible for each selected measure when reporting PQRS data using Claims-Based Reporting (effective Jan 1, 2011; previously was 80%). A claim is considered "eligible" in PQRS when the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis and the CPT® Category I evaluation and management (E/M) codes on the claim match the diagnosis and encounter codes listed in the denominator criteria of the measure specification. Note that several measures allow the use of CPT II modifiers.

For 2011, there are approximately 19 individual measures and 2 measures groups that are relevant to ACCP members. The two measures groups are the community-acquired pneumonia (CAP) and asthma (new this year) measures groups. The CAP measures group bundles **#56** Vital Signs, **#57** Assessment of Oxygen, **#58** Assessment of Mental Status, and **#59** Empiric Antibiotic Prescribed. The asthma measures group bundles **#53** Asthma Pharmacologic Therapy, **#64** Asthma Assessment, **#231** Asthma: Tobacco Use Screening – Ambulatory Care Setting, and **#232** Asthma: Tobacco Use Intervention – Ambulatory Care Setting.

PQRS data submission is as simple as adding a code to existing claims that have specified ICD-9-CM diagnostic codes and E/M codes. For example, to indicate that you reviewed and documented spirometry results for a COPD patient, just add **3023F** to the claim form with $0.00 in the payment field.

Measures groups simplify PQRS reporting even further. For example, if all quality actions for the applicable measures in the CAP measures group (**#56-#59**) have been performed for a patient, just add to the existing claim form **G8550** with $0.00 in the payment field. The ACCP is working toward attaining new measures groups relevant to its members for the coming years.

Each measure has a reporting frequency requirement (called a "measure tag") for each eligible patient seen during the reporting period for each individual physician. The reporting frequency is found in the instructions section of each measure specification. Ensure that all members of the team understand and capture this information in the clinical record.

The ACCP recommends beginning implementation of PQRS participation as soon as possible, if your practice has not already done so. We recommend referencing chapters 1, 2, and 27 of *Coding for Chest Medicine 2011* for more information. An excerpt adapted from Chapter 1, Attachment A of *Coding for Chest Medicine 2011* is provided in the box above to assist practices that have not yet begun PQRS implementation. ■

For assistance, contact the ACCP coding and reimbursement consultant staff, Diane Krier-Morrow, MBA, MPH, CCS-P, at (847) 677-9464 or dkriermorr@aol.com*; or contact QualityNet Help Desk:* qnetsupport@sdps.org *or (866) 288-8912.*

URLs of Relevant Documents

▶ **2011 Medicare Physician Fee Schedule Final Rule (CMS-1503-FC)**
edocket.access.gpo.gov/2010/pdf/2010-27969.pdf

▶ **CMS PQRS Web Page**
cms.gov/pqrs

▶ **2011 Physician Quality Reporting System Measure Specifications and Release Notes**
cms.gov/pqri/downloads/2011_PhyQualRptgSystemMeasureSpecsandReleaseNotes12222010.zip

▶ **List of Eligible Professionals (EPs) for PQRS**
cms.gov/pqri/downloads/EligibleProfessionals.pdf

Steps to PQRS Participation

1. Select an employee to lead implementation.
2. Review all Centers for Medicare & Medicaid Services (CMS) specifications and decide which performance measures (at least 3 individual) or group measures (at least 1) (CAP and/or Asthma) to report.
3. Augment current charge capture and other practice processes to incorporate PQRS measures—eg, revise encounter form to include selected measures (include relevant HCPCS Category II codes or G performance measure codes), and prompt providers to document performance of the measure.
4. Select the reporting period: Claims and registry-based reporting have a Jan 1 or July 1 start date; EHR-based, eRx, and group practice reporting options have a Jan 1 start date.
5. Report $0.00 in the payment field.
6. Audit the claim forms to ensure correct reporting before submission.
7. Have practice (coding, billing, or supervisory) staff regularly and routinely monitor that the providers reporting PQRS measures are reaching appropriate thresholds—changed from 80% to 50% of the applicable population of patients with the diagnoses of asthma, COPD, or pneumonia (when using claims-based reporting).
8. Have practice staff monitor and follow up on Medicare Summary Notices (MSNs) to verify the presence of the N365 code, which indicates process and transmission of the Quality-Data Code.
9. Review each of the steps at monthly departmental meetings.

FROM THE DESK OF THE PRACTICE MANAGEMENT COMMITTEE

Introduction to Current Procedural Terminology (CPT®)

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

Current Procedural Terminology (CPT®) is a listing of descriptive terms and identifying codes for reporting medical services and procedures. CPT was developed in 1966 by the American Medical Association (AMA) to standardize documentation and communication between health-care providers, third parties, and patients. It is now the most commonly accepted medical terminology used to report procedures and services to public (ie, Medicare, Medicaid) and private insurers. The AMA publishes an updated *CPT* coding book annually.

There are three categories of CPT codes. Category I codes report a procedure or service, eg, new for 2011 is CPT **31634** for balloon occlusion. For a procedure or service to be reimbursed, the correct Category I code needs to be submitted to the payor. Category II codes are supplemental tracking codes that can be used for performance measures, with the purposes of decreasing the need for chart review and manual data collection. The Physician Quality Reporting System (PQRS) codes are included in CPT Category II. Category III are temporary tracking codes for new and emerging technologies, eg, five new codes for 2011 are **0243T-0244T** for acoustic PFTs and **0250T-0252T** for bronchial valves. The main purpose of Category III codes is to facilitate assessment of new services and procedures.

CPT is maintained by the CPT Editorial Panel, which is composed of 17 members: 11 representing medical specialty societies, two nominated by insurance companies, one by CMS, one by hospitals, and two by nonphysician providers. The CPT Editorial Panel is authorized to revise, update, or modify CPT codes. This committee controls the code numbers, code descriptions, and code categorization but is not in charge of code valuation. That responsibility is held separately by the AMA/Specialty Society RVS Update Committee (RUC).

The CPT Editorial Panel is supported by the CPT Advisory Committee, which is much broader, having representatives from all national medical specialty societies who are also represented in the AMA House of Delegates. Dr. Steven G. Peters, FCCP, is the ACCP representative on the CPT Advisory Committee, and Dr. Michael E. Nelson, FCCP, is the Alternate ACCP CPT Advisor.

The ACCP Practice Management Committee (PMC) is the group that represents ACCP members' interests regarding the CPT processes. The ACCP PMC proposes new CPT codes, recommends revisions to existing CPT codes, comments on relevant submissions from other specialty societies, and also reviews and chooses whether or not to endorse proposals from drug and device manufacturers. The ACCP PMC represents ACCP in several other ways in addition to CPT, such as representing ACCP members' interests regarding RUC. ACCP members may submit CPT proposal suggestions to the ACCP PMC by e-mailing Marla Brichta at MBrichta@chestnet.org.

In May's *CHEST PHYSICIAN,* we will be explaining the PMC's work with the AMA/Specialty Society Relative Value Scale (RVS) Update Committee (RUC) that recommends values to Medicare for new and revised CPT codes. ■

Pages 6a—6f

The CHEST Foundation 2011 Awards Program

Don't miss this opportunity! Application deadline is May 4, 2011.

The CHEST Foundation offers ACCP members opportunities to apply for awards in the areas of clinical research, leadership in end-of-life care, and humanitarian service.

New for 2011! OneBreath™ Clinical Research Award in Lung Cancer
This $100,000 award ($50,000 each year for 2 years) supports an ACCP member's project that is focused on medical and/or surgical detection, or treatment of lung cancer based on clinical/translational research. It is available to an ACCP member (Affiliate Members eligible) who has completed at least 2 years of pulmonary or critical care fellowship or a thoracic surgery residency and is within 7 years of completing training.

The CHEST Foundation and the Respiratory Health Association of Metropolitan Chicago Clinical Research Award in Women's Lung Health
This $10,000 award supports a clinical research project related to women's lung health, which may include research on gender differences in various lung diseases, such as COPD and lung cancer. It is available to an ACCP member holding the degree of MD, DO, MBBCh, PharmD, PhD, or equivalent.

The CHEST Foundation California Chapter Clinical Research/Medical Education Award
This $5,000 award supports a 1-year clinical research or medical education project proposed by an ACCP member who lives in California. ACCP members, including Affiliate Members, holding the degree of MD, DO, MBBCh, PharmD, PhD, or the equivalent are eligible.

Roger C. Bone Advances in End-of-Life Care Award
This $10,000 grant supports leadership in end-of-life care by stressing the importance of communication, compassion, and effective listening. The award is given for leadership in end-of-life care on the international, national, or local level. It is available to an ACCP member holding the degree of MD, DO, MBBCh, PharmD, PhD, or the equivalent.

Alpha-1 Foundation and The CHEST Foundation Clinical Research Award in COPD and Alpha-1 Antitrypsin (AAT) Deficiency
This $25,000 award supports research focused on COPD and AAT deficiency. Research projects primarily in usual COPD (not associated with AAT deficiency) are allowed. Projects focusing on AAT deficiency are encouraged. ACCP members, including Affiliate Members, holding the degree of MD, DO, MBBCh, PharmD, PhD, or the equivalent are eligible.

Association of Specialty Professors and The CHEST Foundation of the ACCP Geriatric Development Award
This $50,000 award (with $100,000 NIH GEMSSTAR grant) supports career development for junior faculty in the early stages of their research career in geriatrics. *Important note:* To be eligible for this award, you must have first applied for the GEMSSTAR award through the National Institute on Aging and received a fundable score.

Third GlaxoSmithKline Distinguished Scholar in Thrombosis
This $150,000 award ($50,000 each year for 3 years) supports an ACCP Fellow (FCCP) who proposes a thrombosis-related project/service that investigates treatment alternatives; educates patients; disseminates new knowledge; addresses family, legislative, and regulatory issues; or defines new mechanisms leading to treatment innovations and improvements. To be eligible, the FCCP must hold the degree of MD, DO, MBChB, MBBCh, MBBS, DNSc, Pharm D, PhD, or EdD.

D. Robert McCaffree, MD, Master FCCP Humanitarian Awards
Multiple awards totaling up to $50,000 are given for community-based projects supported by the pro bono work of ACCP members worldwide. Projects must show a clear impact on the community and have the potential for long-term sustainability and replicability. Award funds are paid to the nonprofit or nongovernmental organization where the ACCP member donates time and medical service. All ACCP members, including Affiliate Members and Allied Health Members, are eligible to apply, but applicants must be a current member for at least 2 years. ■

Learn more about the 2011 awards at OneBreath.org, *or go to the submission site at* mc.manuscriptcentral.com/chest2011. *Contact Lee Ann Fulton at* lfulton@chestnet.org *with questions.*

observed in an additional 22 patients 12 to 17 years of age who were treated with DULERA in another clinical trial. The safety and efficacy of DULERA have not been established in children less than 12 years of age.

Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in growth velocity in pediatric patients. In these studies, the mean reduction in growth velocity was approximately 1 cm per year (range 0.3 to 1.8 per year) and appears to depend upon dose and duration of exposure. This effect was observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for "catch up" growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied.

The growth of children and adolescents receiving orally inhaled corticosteroids, including DULERA, should be monitored routinely (e.g., via stadiometry). If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect should be considered. The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of orally inhaled corticosteroids, including DULERA, each patient should be titrated to his/her lowest effective dose *[see Dosage and Administration (2.2)]*.

8.5 Geriatric Use

A total of 77 patients 65 years of age and older (of which 11 were 75 years and older) have been treated with DULERA in 3 clinical trials up to 52 weeks in duration. Similar efficacy and safety results were observed in an additional 28 patients 65 years of age and older who were treated with DULERA in another clinical trial. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As with other products containing $beta_2$-agonists, special caution should be observed when using DULERA in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by $beta_2$-agonists. Based on available data for DULERA or its active components, no adjustment of dosage of DULERA in geriatric patients is warranted.

8.6 Hepatic Impairment

Concentrations of mometasone furoate appear to increase with severity of hepatic impairment *[see Clinical Pharmacology (12.3)]*.

10.1 Signs and Symptoms

DULERA: DULERA contains both mometasone furoate and formoterol fumarate; therefore, the risks associated with overdosage for the individual components described below apply to DULERA.

Mometasone Furoate: Chronic overdosage may result in signs/symptoms of hypercorticism *[see Warnings and Precautions (5.7)]*. Single oral doses up to 8000 mcg of mometasone furoate have been studied on human volunteers with no adverse reactions reported.

Formoterol Fumarate: The expected signs and symptoms with overdosage of formoterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the following signs and symptoms: angina, hypertension or hypotension, tachycardia, with rates up to 200 beats/min., arrhythmias, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, and insomnia. Metabolic acidosis may also occur. Cardiac arrest and even death may be associated with an overdose of formoterol.

The minimum acute lethal inhalation dose of formoterol fumarate in rats is 156 mg/kg (approximately 63,000 times the MRHD on a mcg/m^2 basis). The median lethal oral doses in Chinese hamsters, rats, and mice provide even higher multiples of the MRHD.

10.2 Treatment

DULERA: Treatment of overdosage consists of discontinuation of DULERA together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of DULERA. Cardiac monitoring is recommended in cases of overdosage.

Manufactured by 3M Health Care Ltd.,
Loughborough, United Kingdom.
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MERCK & CO., INC.
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6/10 **32704107T-JBS**

Pulmonary Perspectives

The Rigid Bronchoscope: A Pulmonologist's 'Forgotten Tool'?

Since its first reported use to remove a foreign body from the airways by Gustav Killian in 1897, rigid bronchoscopy (RB) has been used successfully for other airway diseases. Airway visualization by bronchoscopy was a technique initially performed almost exclusively by surgeons until the introduction of the flexible bronchoscope in 1966. The flexible bronchoscope replaced the use of rigid bronchoscopes and defined the modern era of pulmonary medicine. In the early 1980s, physicians realized that there were advantages to rigid bronchoscopy for interventional procedures, such as the endobronchial management of lung cancer, critical airway obstruction, and other airway diseases. Furthermore, new indications and modalities are still being developed. Despite the advantages of rigid bronchoscopy, only 4% of pulmonologists who responded to a survey reported that they used a rigid bronchoscope in their practice (Colt et al. *J Bronchol.* 2000;7:8), though interventional pulmonologists, thoracic surgeons, and otolaryngologists use rigid bronchoscopes on a regular basis. Unfortunately, many pulmonologists finish their training with insufficient knowledge about the indications and uses of rigid bronchoscopes. Different interventional pulmonology programs and bronchoscopy organizations are trying to encourage the use of rigid bronchoscopes by creating fellowships and sponsoring hands-on courses. However, due to the complexity of this procedure and the methods of teaching needed, some will not gain this proficiency. It is the goal of this article to heighten the interest of the pulmonary community to explore and learn more about this "old" instrument.

Fig 1. A rigid bronchoscope (top) has openings in the distal end to allow ventilation to the contralateral lung; a tracheoscope (bottom) lacks these holes.

PHOTOS COURTESY DR. JAVIER I. DIAZ-MENDOZA

Fig 2. The proximal part of rigid bronchoscope has multiple ports: The ones on the lower side are for ventilation; those on the upper side are for instrumentation.

History and Equipment

Manuel Rodriguez Garcia, a Spanish singer and music teacher, was the first to perform an "in vivo" visualization of the airways by studying his own larynx in 1855. Johann Czermak perfected the technique for indirect laryngoscopy in Germany in 1858. The first use in America was by Horace Green, the "father of laryngology," to make laryngeal applications of silver nitrate (Bryce et al. *The American Laryngological Association 1878-1978: A centennial history*. Washington, DC: The Association; 1978).

It was not until 1895 in Germany that Alfred Kirstein performed the first direct examination of the larynx by using a rubber tube with an electric bulb. One of his pupils, Gustav Killian, subsequently performed the first rigid bronchoscopy to remove a foreign body from a patient who had aspirated a bone into his right main bronchus (Zollner F. *Arch Otolaryngol* 1965;82[6]:656). Later, Killian was named the "father of bronchoscopy." Around the same time, Chevalier Jackson, an American laryngologist from Pennsylvania, started to develop his own endoscopes with distal illumination; he used them initially with dogs and inanimate models. He published his book, *Tracheobronchoscopy, Esophagology and Bronchoscopy,* in 1907; later, he was considered the "father of American bronchoesophagology" (Jackson. *The life of Chevalier Jackson: an autobiography*. New York, NY: MacMillan; 1938).

E. Broyles introduced the telescope optic for bronchoscopy in Baltimore in 1940, followed by the optical forceps (1948). Shigeto Ikeda from Japan, who later developed the flexible fiberscope, introduced glass fiber illumination for the rigid bronchoscope in 1962.

Hopkins, in England, developed a rod-lens telescope system that considerably improved the lighting and imaging through the rigid bronchoscope (1954). This technology was adopted by K. Storz as a cold light illumination source for his rigid bronchoscopes in 1963 (Bolliger et al. *Interventional bronchoscopy*. Basel, Switzerland: S Karger Publishers; 2000).

Though minor adjustments have been made to the equipment since then, today's rigid bronchoscopes are similar to those used in the days of Jackson. They are stainless steel, tapered tubes with a flared and beveled distal tip. The proximal end of the bronchoscope consists of a central opening and several side ports that are used for ventilation tubes and instrumentation. The typical "light carrier" is a thin glass rod (telescope) connected to a proximal light source through a fiberoptic cable. Bronchoscopes have slit-like openings in the distal end that allow ventilation to the contralateral lung, while tracheoscopes lack these side holes and are shorter. The diameter of rigid bronchoscopes ranges from 9 to 14 mm, which allows the passage of multiple instruments simultaneously, such as suction catheters, laser fibers, forceps, and flexible bronchoscopes, among others (Figs 1-3).

Fig 3. A rod-lens telescope can be introduced into the rigid scope; a light source connects to inferior part of telescope. Visualization is done through the black port.

Anesthesia

Preoperative patient preparation for RB includes restricted oral intake for at least 6 hours before the procedure and correction of coagulopathies. The use of agents to decrease bronchial secretions is not routinely required.

Even though the technique for RB has remained almost the same since the late 19th century, the anesthetic technique has changed considerably. Jackson described the use of hypodermic morphine sulfate combined with topical cocaine as adequate to perform RB (Jackson. *Bronchoscopy and esophagoscopy*. Philadelphia, PA: J B Saunders Company; 1927).

Currently, general anesthesia is preferred for the comfort and safety of the patient. Communication and coordination between the bronchoscopist and the anesthesiologist is crucial before, during, and after the procedure. Anesthesia induction can be done via inhaled sevoflurane (usually in critical airway stenosis) or by administration of IV agents like ramifentanyl and propofol (Perrin et al. *Chest*. 1992;102[5]:1526). Muscle relaxants, like succinylcholine, are commonly used during the initial

Indications for Rigid Bronchoscopy

Diagnostic

- Massive hemoptysis
- Endobronchial biopsies (large specimens)

Therapeutic

- Foreign body removal
- Airway obstruction: malignant and benign
- Ablative techniques: mechanical, laser, electrocautery, argon plasma coagulation, cryotherapy
- Airway stenting: airway obstruction, tracheomalacia, tracheoesophageal fistula
- Tracheobronchoplasty with balloon

Dr. Marilyn G. Foreman, FCCP
Editor, *Pulmonary Perspectives*

Dr. Loren J. Harris, FCCP
Deputy Editor, *Pulmonary Perspectives*

bronchoscope insertion. Ventilation can be spontaneous-assisted ventilation, in which the anesthesiologist provides frequent assisted breaths and works to synchronize breathing with the bronchoscopist's maneuvers. Venturi jet ventilation is another modality adopted by many centers, due to its advantages for oxygenation and to overcome the increased airway resistance that occurs with telescope use (Godden et al. *Thorax*. 1982;37[7]:532). Postprocedure care is done in a recovery room under strict monitoring. Most rigid bronchoscopic procedures are ambulatory.

Intubation Technique

The position of the patient is very important in order to achieve successful intubation with the rigid bronchoscope. The patient should be positioned supine with extension of the neck, allowing alignment of the pharynx, larynx, and trachea. Some techniques use a laryngoscope as an aide for intubation, others use an initial placement of an endotracheal tube that then is used as a guide for intubation, and others use only the rigid bronchoscope with or without the use of a Hopkins telescope.

Once the bronchoscope is passed into the trachea, the central airways can be visualized. Segmental airways are difficult to evaluate unless an angled telescope or a flexible bronchoscope is used through the rigid bronchoscope.

Indications and Contraindications

Even though flexible bronchoscopy is indicated in the diagnosis and management of different pulmonary diseases, there are still multiple conditions in which RB is preferred over flexible bronchoscopy, ie, the management of massive hemoptysis, removal of foreign bodies, and malignant airway obstruction. Moreover, some therapeutic techniques, like the placement of silicone stents for tracheal stenosis, tracheobronchomalacia, and malignant airway obstruction, can only be performed with a rigid bronchoscope.

Since general anesthesia is typically needed, contraindications for RB are related to comorbid diseases that increase the risk of anesthesia. An absolute contraindication includes cervical spine disease, which prevents positioning of the neck (Wain. *Chest Surg Clin N Am*. 2001;11[4]:691).

Complications

In experienced hands, the complications of RB are rare. The most common ones are related to trauma of the upper airways, including the oropharynx and teeth (Ayers and Beamis. *Clin Chest Med*. 2001;22[2]:355). Massive hemoptysis is very rare. Cardiac arrhythmias and respiratory depression can be seen due to anesthesia. Only two deaths were reported after 11,000 rigid bronchoscopies (Caputi et al. *Panminerva Med*. 1986;28[3]:271).

Conclusion

The use of RB decreased after the introduction of flexible bronchoscopy. Despite being a safe procedure and having solid indications in the management of pulmonary diseases, most pulmonologists do not perform RB; furthermore, many of them have no exposure to RB during their training. It is important to stimulate the interest of pulmonologists to prevent RB from becoming a "forgotten tool." ■

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and
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Senior Staff Physician
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Editor's Insight

This article provides a historical review of rigid bronchoscopy and highlights its importance in the future of pulmonary medicine. The introduction of flexible bronchoscopy brought about a rapid decline in the number of physicians performing and teaching the technique of rigid bronchoscopy. Over the past 20 years, however, the growing field of interventional pulmonary medicine has brought the rigid bronchoscopist back from the "brink of extinction" by defining the criteria for certification and indications for use (Ernst et al. *Chest*. 2003;123[5]:1693; and Bolliger et al. *Eur Respir J*. 2002;19[2]:356). This review should serve as a call to action to incorporate rigid bronchoscopy into the basic training of a bronchoscopist, especially at those institutions where high-grade airway obstruction, massive hemoptysis, and stent deployment and removal are commonplace.

—Dr. Eric L. Flenaugh, FCCP
Georgia Cancer Coalition's Distinguished Cancer Clinician & Scholar,
Director of Advanced Diagnostic and Interventional Pulmonary Medicine,
Georgia Cancer Center of Excellence and Morehouse School of Medicine,
Atlanta, GA

Editor's note: *Because I was not trained in rigid bronchoscopy and RB is not performed by thoracic surgery at my institution, commentary for this article was invited and provided by a guest editor.*

Centers of Excellence

New at CHEST 2011, in Honolulu, HI, the ACCP will offer selected hospitals, non-hospital-based medical practices, and companies a special opportunity to showcase programs and practices that improve health-care outcomes. We plan to call this space "Centers of Excellence and Non-Hospital-Based Best Practices" (COE).

The COE will be held in a dedicated area adjacent to, but separated from, the Clinical Resource Center (exhibit hall). The COE will contain up to 10 hospitals and non-hospital-based practices, along with 10 "touchdown stations," for close interaction with attendees, all selected by a special ACCP committee. The touchdown station will serve as a special space, allowing a company to present its role toward helping the COE achieve its goal.

The College views this as a unique opportunity for hospitals and other practice sites to showcase why they were selected as the "Best of the Best."

The Centers of Excellence will offer a VIP opening on Saturday or Sunday evening and will welcome other attendees and non-CHEST registrants until the Clinical Resource Center closes on Wednesday. Updates on selected COE will be listed in future articles. ■

Get up-to-the-minute details on CHEST 2011 at www.accpmeeting.org.

This Month in *CHEST:* Editor's Picks

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

▶ **COPD in Never Smokers: Results From the Population-Based Burden of Obstructive Lung Disease Study.** *By Dr. B. Lamprecht et al.*
▶ **Effects of Water-Pipe Smoking on Lung Function: A Systematic Review and Meta-analysis.** *By Dr. D. Raad et al.*
▶ **The Acute Effects of Water-Pipe Smoking on the Cardiorespiratory System.** *By Dr. F. Hakim et al.*
▶ **Elevated Pulmonary Artery Pressure Is a Risk Factor for Primary Graft Dysfunction Following Lung Transplantation for Idiopathic Pulmonary Fibrosis.** *By Dr. A. Fang et al.*
▶ **ICU Care Associated With Symptoms of Depression and Posttraumatic Stress Disorder Among Family Members of Patients Who Die in the ICU.** *By Dr. E. K. Kross et al.*

SPECIAL FEATURE
▶ **COPD in China: The Burden and Importance of Proper Management.** *By Dr. X. Fang et al.*

COMMENTARY
▶ **Apologizing for Humiliations in Medical Practice.** *By Dr. A. Lazare and Ms. R. Sherman Levy.*

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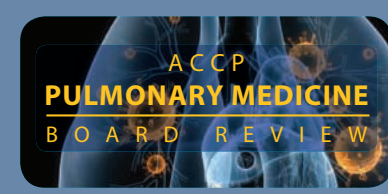

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Critical Care Commentary

Interventional Pulmonology: Advanced Bronchoscopy in the Critically Ill

The interventional pulmonologist plays an integral role in the management of critically ill patients with respiratory failure due to central airway obstruction, massive hemoptysis, and complications of thoracic surgery or radiation therapy. Bronchoscopy offers a minimally invasive diagnostic and therapeutic tool to palliate airway obstruction, providing symptomatic relief and potentially serving as a means to extubation.

Interventional pulmonology (IP) is a rapidly growing field that focuses on minimally invasive diagnostic and therapeutic techniques for complex airway, mediastinal, lung, and pleural diseases. The interventional pulmonologist is trained in pulmonary medicine and critical care medicine, with subsequent dedicated fellowship training in IP (Lamb et al. *Chest*. 2010;137[1]:195). Interventional bronchoscopy requires skills to manage the complex airway with both flexible and rigid bronchoscopy, as well as mechanical ventilation.

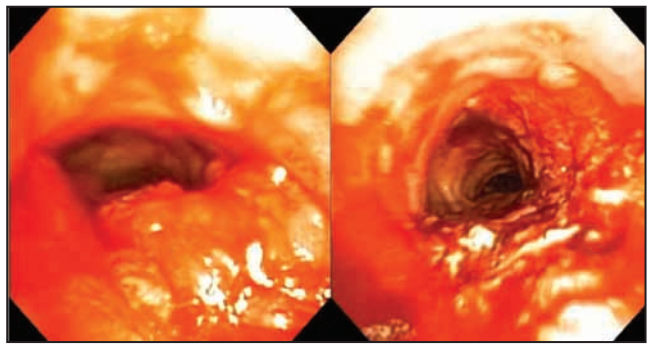
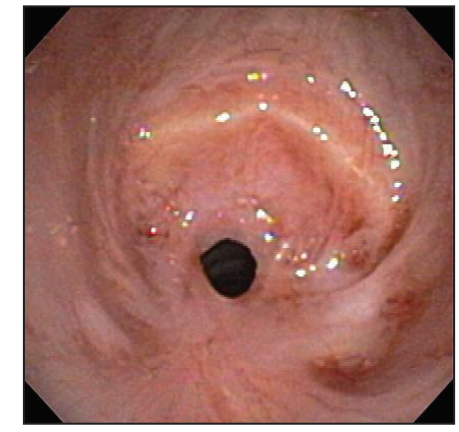


Fig 2. Mechanical core-out and debulking can treat tracheal obstruction due to carcinoma of the esophagus.

Safe rigid bronchoscopy for foreign body removal was introduced by Gustav Killian, a laryngologist, in 1897 (Becker. *J Bronchol*. 1995;2:77). Rigid bronchoscopy began to diminish as a useful modality in the decades after the introduction of the flexible bronchofiberscope by Ikeda in 1962. An ACCP survey of North American pulmonary bronchoscopists published in 1991 revealed that 91.6% did not perform rigid bronchoscopy routinely in practice (Prakash et al. *Chest*. 1991;100[6]:1668). Although flexible bronchoscopy dramatically changed the field of pulmonary medicine, IP has recently reinvigorated the use of rigid bronchoscopy to augment management of central airway obstruction.



Images courtesy Dr. Mohit Chawla

Fig 1. Tracheal stenosis can be treated with bronchoscopic dilatation.

Managing Central Airway Obstruction

A small percentage of respiratory failure is due to central airway obstruction. Airway obstruction may be due to a multitude of causes, whether benign or malignant, endoluminal or extrinsic, mechanical or functional. A high degree of morbidity is associated with such airflow obstruction (Ernst et al. *Am J Respir Crit Care Med*. 2004;169[12]:1278). The "reserve" in airway diameter is so great that exertional symptoms may not be present until a loss of approximately 50% is experienced, roughly 7 to 10 mm at the level of the trachea. Failure to extubate a patient may reflect tracheal pathology, such as dynamic airway collapse or tracheal stenosis. Artificial airways may bypass central airway obstructions, therefore limiting the benefit of ventilator waveforms. CT scanning with both dynamic imaging (Lee et al. *Chest*. 2007;131[3]:758) and 3-D reconstruction has greatly advanced examining the airway anatomy. CT virtual bronchoscopy affords noninvasive diagnostics of airway patency (Boiselle et al. *Respiration*. 2003;70[4]:383). However, bronchoscopy remains the gold standard for direct visual inspection of airway obstruction.

In the management of malignant airway obstruction, bronchoscopy is often palliative and serves as a bridge to further oncologic therapy. This can often be implemented in conjunction with external beam radiation therapy or systemic chemotherapy. In benign airway obstruction, such as tracheal stenosis or tracheobronchomalacia, bronchoscopy can palliate the airway with temporizing measures, such as balloon dilatation or airway stenting.

Anesthetic choices and airway control are of key importance when approaching the patient with central airway obstruction. There must be constant communication between the bronchoscopist and the intensivist or anesthesiologist. In high-grade obstruction, rigid bronchoscopy is the instrument of choice, as you can bypass the obstruction under visualization, and it offers a secure airway with the ability to ventilate. Ventilation can be achieved with either an open circuit (jet ventilation) or a closed circuit (volume- or pressure-control). Hand-ventilation may offer a lower risk of barotrauma and the ability to identify changes, such as an acute obstruction, more readily.

If there are no immediate options for surgical resection, obstructions are best handled by rigid bronchoscopy in an operating room. Inevitably, flexible bronchoscopy is also required to navigate beyond obstructions for planning, examining distal airways, and cleaning the airways of secretions or blood.

Mechanical Debulking, Bronchoplasty, and Ablative Bronchoscopy

For patients in respiratory failure, "therapeutic," or palliative, bronchoscopy can lead to successful extubation in select patients, decreased hospitalization, and lower health-care costs (Colt et al. *Chest*. 1997[1];112:202). If airway patency can be regained, then there is a greater chance of liberation from mechanical ventilation. Therapeutic bronchoscopy often provides a bridge to the institution of further therapies, such as radiation therapy or chemotherapy. Malignant airway obstruction can be relieved with mechanical efforts or ablative interventions. The mechanical approach focuses upon "core-out" or forceps debulking, when the obstruction is endoluminal, and may or may not include ablative therapies. This acute

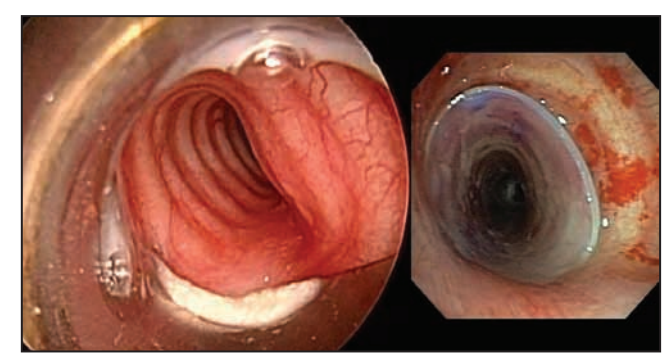


Fig 3. Silicon Y-stenting is useful for extrinsic compression of trachea and right mainstem bronchus from sarcoma.

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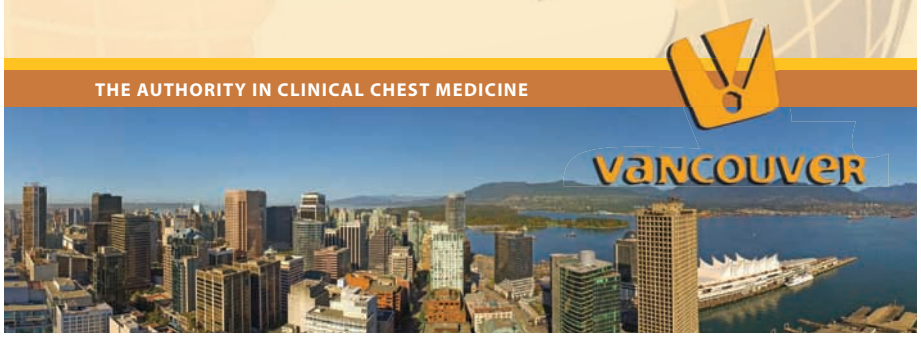

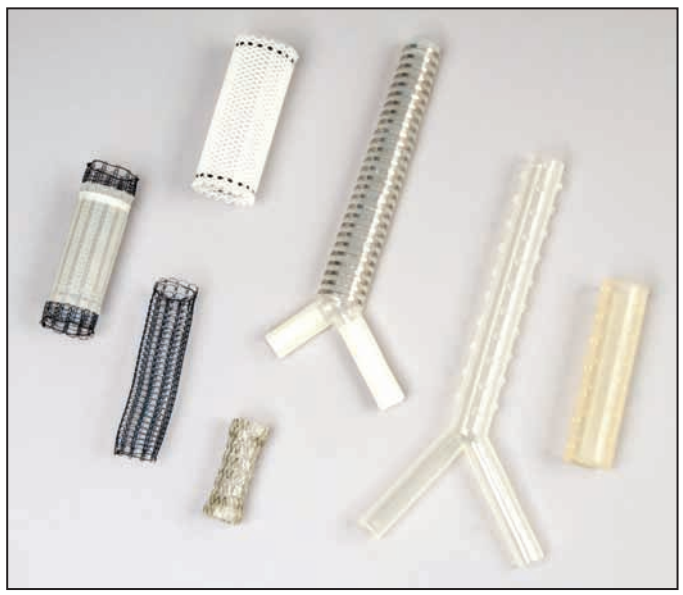

Fig 4. The various types of available airway stents include self-expanding metallic, silicon, and hybrid.

relief minimizes postobstructive manifestations, stabilizes the airway, and minimizes tumor burden for external beam radiation therapy (Eichenhorn et al. *Chest*. 1986;89[6]:782). In benign obstructions, such as tracheal stenosis (Fig 1) seen with the prolonged use of artificial airways, bronchoscopic dilatation with serial rigid bronchoscopes, dilators, or balloons can palliate the airway. Although there are limited survival data, relief of airway obstruction (Fig 2) leads to relief of symptoms, in most cases.

Multiple modalities are available for thermal ablation of endobronchial neoplasm. These are safely implemented if the FIO_2 can be safely reduced below 0.4 to avoid airway fires. Nd:YAG laser is probably the most established. Through photocoagulation and photonecrosis, Nd:YAG laser devascularizes the tumor, allowing the bronchoscopist to encounter less bleeding during subsequent mechanical debulking. Following combined modality bronchoscopy, patients experience palliation of symptoms, such as cough and dyspnea with low morbidity; however, there are still only limited studies that show the quantitative improvement in quality of life with validated measures (Mantovani G et al. *Clin Lung Cancer*. 2000;1[4]:277).

DR. NEIL HALPERN, FCCP
Section Editor,
Critical Care Commentary

Airway Stents

Although bronchoscopic palliation of malignant airway obstruction can be achieved with mechanical and ablative means alone, debulking may not always be feasible. Airway integrity can also be impaired by extrinsic compression (Fig 3). In these circumstances, stents of various kinds (Fig 4) can be placed to support the airways. In certain cases of respiratory failure, stents in conjunction with endotracheal intubation may facilitate liberation from the ventilator. Great care and thought must be taken before deciding to place a stent but also in choosing the stent type (metallic, silicon, or hybrid) (Lund et al. *Chest*. 2007; 132[4]:1107). Although of relatively low risk, stents should not be placed in all situations of airway obstruction. Complications of stent insertion include in-stent obstruction due to mucous plugging or granulation tissue, stent migration, and, less often, airway perforation secondary to a fractured metallic stent. Stents themselves may extend benign focal stenoses into longer areas of scar, rendering them unresectable (Grillo. *Ann Thorac Surg*. 2000;70[4]: 1142). If surgical resection is feasible, then stent placement may not be appropriate; or if a stent was already inserted, it should be removed as early as possible.

Managing Hemoptysis

Large-volume hemoptysis can be seen in malignancy or its treatment, bronchiectasis, vascular anomalies, and other disease states. Radiographic imaging may not reveal the bleeding source, thus localization and possible intervention with bronchoscopy may be required. Ablative therapies for endobronchial malignancy can be implemented; however, tamponade with blocker devices or instillation of epinephrine or thrombin is often required to temporize bleeding. Although smaller bleeds may be handled with the flexible bronchoscope, it is most prudent to utilize rigid bronchoscopy for definitive airway control and tamponade, as well as ease of suction. Often, bronchoscopy complements or guides angio-invasive procedures for definitive control of vascular sources.

Surgical and Radiation Catastrophes

Respiratory failure may present as a complication of lung surgery, such as surgical stump breakdown or bronchial fistula. Airway or alveolar fistulae, as a result of malignant involvement, may also occur following external beam radiation to thoracic structures or after percutaneous thermal ablation. These conditions can often be successfully managed via bronchoscopy as a less invasive alternative to operative interventions with low morbidity, especially if surgical repair is not feasible or advised.

Summary

Central airway obstruction can be life-threatening and, often, patients require mechanical ventilation and ICU care. Immediate bronchoscopic palliation offers the intensivist an opportunity to extubate and minimize health-care costs, as well as ICU length of stay (Colt et al. *Chest*. 1997;112[1]:202). Adverse events related to bronchoscopy and interventions, such as stent migration, mucous plugging of stents, or hemoptysis, obligate the interventionalist to always be available. The realm of IP is broad across bronchoscopy (see box), with limited outcomes data. As part of their quality improvement initiative, the American College of Chest Physicians has undertaken prospective data collection of diagnostic and interventional bronchoscopy outcomes based upon the work of several international IP programs (Ernst et al. *Chest*. 2008;134[3]: 514). Interventional bronchoscopy offers minimally invasive therapies at all levels of disease safely and effectively. ■

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Memorial Sloan-Kettering Cancer Center
New York, NY

The Realm of Interventional Pulmonology

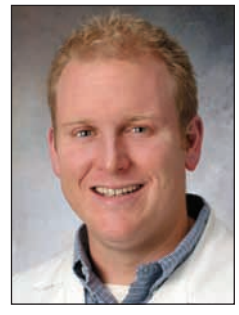
Advanced Diagnostic Bronchoscopy
- Transbronchial biopsy
- Transbronchial needle aspiration (TBNA)
- Endobronchial ultrasound (EBUS), convex and radial probe
- Thoracic fluoroscopy
- Electromagnetic and virtual navigational bronchoscopy
- Autofluorescence bronchoscopy (AF)
- Narrow band imaging (NBI)
- Endoscopic optical coherence tomography
- Endocytoscopy
- Alveoloscopy and fibered confocal microendoscopy

Therapeutic Bronchoscopy and Artificial Airways
- Airway stents: self-expanding metallic, silicon, and hybrid; placement and removal
- Balloon bronchoplasty and mechanical airway dilatation
- Laser bronchoscopy, Nd:YAG, and KTP
- Electrocautery
- Argon plasma coagulation (APC)
- Cryotherapy
- Endobronchial brachytherapy
- Photodynamic therapy
- Endoscopic abscess drainage
- Fistula and stump closure
- Foreign body removal
- Percutaneous tracheostomy
- T-tube placement
- Transtracheal oxygen
- Intrabronchial one-way valves
- Endoscopic lung volume reduction
- Bronchial thermoplasty
- Whole lung lavage

CHEST Podcasts: If You Missed It

The *CHEST* journal kicked off its inaugural podcast in the March issue with an intriguing discussion about ventilator-associated tracheobronchitis.

Each month, podcast editor Dr. D. Kyle Hogarth, FCCP, will moderate a dialogue between the author of an original research article and the corresponding editorial published in that issue.



DR. D. KYLE HOGARTH

Dr. Hogarth explained the aim of the podcasts this way: "The goal of each conversation is to pique the listeners' interest and compel them to go out and read additional work by the featured authors and about their topics of interest."

Visit *CHEST* online each month at www.chestpubs.org to hear these thoughtful, in-depth discussions of the most pressing issues facing clinicians in chest medicine. ■

Past ACCP President Remembered

Dr. Marvin Dunn, Master FCCP, passed away on February 16, 2011. A former Dean of the University of Kansas (KU) School of Medicine, and an internationally prominent cardiologist, Dr. Dunn served the ACCP as President in 1988-1989. An active ACCP Fellow for many years, he chaired numerous ACCP committees and served on the *CHEST* Editorial Board and as a Governor for Kansas and chair of the Council of Governors. Dr. Dunn received one of the highest ACCP honors, that of Master Fellow, in 2002.

Dr. Dunn led the KU School of Medicine from 1980 to 1984. He received his medical degree from the KU School of Medicine in 1954, and his bachelor's degree from KU in 1950. After completing a residency in Internal Medicine at the KU Medical Center in 1959, he joined the faculty of the Department of Internal Medicine. He was a full professor by 1970, and in 1978, was named the Franklin Murphy Distinguished Professor and head of the cardiology section. Dr. Dunn rose to national and international prominence as a cardiologist who pioneered the development of coronary angioplasty. In his 46 years with the heart program, he mentored more than 90 cardiologists, some of whom now practice in leading heart programs at the KU Medical Center and around the world. ■

NETWORKS

LTOT, Azithromycin in Lung Transplantation

Members in Industry

The Clinical Researcher in Industry

Pharma activities have come under significant scrutiny in recent years for many reasons. Much of it has understandably focused on how information is shared on products for their use and commercialization. However, this spotlight focuses on just one aspect of activity. Many physicians are unaware of the drug development process before commercialization, particularly the activities of physicians as clinical investigators within industry.

Clinical investigators in industry assume many tasks. Depending on the size of the company and project, one physician may do all of them or focus on a single aspect.

Early in projects, clinician investigators work to bridge laboratory experiments and potential effects in human disease. Some clinician investigators focus on phase I studies, where potential drugs are given to humans for the first time. Others focus on phase II and III trials, when the size and scope of drug development expands significantly. Clinician investigators are responsible for ensuring patient safety, as well as scientific rigor, in protocol design, data analysis, and reporting. They incorporate feedback from consulting academic researchers, epidemiologists, regulators, and others to address the right questions and answer them appropriately.

Pharma-sponsored clinical trials are extensively regulated and get considerable review within the company, by external experts, and by regulatory authorities. Good clinical practice guidelines, company standards, regulatory guidance, and practice guidelines are all considered as a protocol is developed. Clinician investigators in industry play important roles in identifying opportunities for potential therapeutic intervention and in the clinical programs to characterize a drug's properties.

Dr. Steven G. Simonson, MHS, FCCP
Steering Committee Member

Practice Operations

2011 Challenges in Operating Your Practice

ACCP NetWorks offer a forum for the membership to discuss specific clinical practice- and business-related issues and challenges. The Practice Operations NetWork (PON) stimulates the exchange of ideas and knowledge between physicians and practice administrators/managers in order to improve patient outcomes, aid in the delivery of prompt service, optimize reimbursement, and increase practice efficiency. The PON is different from the ACCP Practice Management Committee (PMC), in that it allows for broader participation from the general membership.

The collaboration between the PMC and PON increases the overall practice management efforts of the ACCP and strengthens the development of the ACCP practice management resources.

In January 2011, a Chicago area PON subgroup, Pulmonary Administrators/Managers (PAM), met to discuss key issues facing their practices. Another Chicago area meeting is planned for April. If interested in participating in PAM, contact Marla Brichta at MBrichta@chestnet.org.

Key issues discussed were:

- Coding and reimbursement of pulmonary function testing in the office.
- Electronic medical records (EMR) implementation and use; obtaining meaningful use criteria.
- E-prescribing (eRx) CMS program requirement to e-prescribe 10 unique patients by June 2011 to avoid CMS penalties in 2012.
- CMS Physician Quality Reporting System (PQRS) changes for 2011 to obtain CMS bonuses for improved quality of care.
- Optimal use of physician extenders (eg, nurse practitioners, physician assistants, etc) in the practice.
- High-deductible insurance collections.
- Recruitment of new physicians.
- CMS changes in reimbursement for Sleep Services in 2011 (details provided in *CHEST Physician,* February 2011, p. 19, "From the Desk of the Practice Management Committee"; http://accpstorage.org/physician/2011/0211.pdf).

The sharing of ideas and knowledge had an immediate impact on the majority of practices that attended. One specific example is when one practice administrator shared that she had been undercoding PFT services and that the knowledge gained during the PAM meeting will enable her to appropriately increase revenues for her practice.

The PON is an example of how ACCP NetWorks can provide added value to the membership. The Practice Operations NetWork is open to all ACCP members who wish to participate. For more information, please contact Maggie Bochnak at the ACCP at mbochnak@chestnet.org.

Michael K. McCormick, RRT, MBA
Chair, Practice Operations

Respiratory Care

Long-term Oxygen Therapy

The data demonstrating the valuable impact of oxygen administration on patient survival were published in the early 1980s. Despite that history and more recent evidence suggesting the benefit of long-term oxygen therapy (LTOT) in the management of lung diseases, almost 30 years later, many deficits remain in the knowledge of clinicians regarding indications for prescription.

Moreover, rapidly changing technology and the availability of many types of oxygen delivery equipment make it difficult for the practicing pulmonologist to keep up with available devices. Physicians generally prescribe oxygen as a number of liters per minute but may not properly prescribe therapy that takes into account a patient's increased oxygen demands during exercise and, perhaps, during sleep.

For example, patients generally prefer portable oxygen devices, and these devices may perform well when the patient is at rest. However, upon exertion, as both the minute ventilation and respiratory rate increase, many devices will not be adequate.

The Airways Disorders, Allied Health, and Respiratory Care NetWorks assembled a task force to review LTOT. The task force's purpose was to evaluate the indications, prescribing requirements, and available devices for providing LTOT. Their report endeavors to clarify all that the clinician should take into account when prescribing LTOT. The task force hopes to publish the full document on the ACCP Web site for easy accessibility and to also make a summary recommendation on LTOT available in an easy-to-carry format.

Dr. Rubin Cohen, FCCP
Vice-Chair, Airways Disorders

Thoracic Oncology

NetWork Updates

The Thoracic Oncology NetWork develops sessions for annual CHEST meetings, carries out projects aimed at improving the care of patients with thoracic malignancies, and provides an entry point for interested individuals to participate in ACCP activities.

A collaborative project of the ACCP and the Society of Thoracic Surgeons (STS) is approaching completion. This systematic review will summarize available evidence for care of the high-risk, early-stage lung cancer patient. Additionally, NetWork steering committee members will be grading applications for The CHEST Foundation's OneBreath™ Lung Cancer Clinical Research Award (http://onebreath.org). The deadline for applications is May 4, 2011.

Finally, the NetWork is considering a project that would propose quality measures for lung cancer care. This is critical, as third-party payers increasingly focus on quality of care.

The NetWork generated several sessions for CHEST 2011 in Honolulu, HI. These include NetWork Highlights, "Becoming More Personal: What We Know, and What We Don't Know About Individualized Therapy for Lung Cancer," and "Radiation From Medical Imaging: How Much Cause for Concern?"

We strongly encourage all interested individuals to attend the NetWork open meeting, featuring Dr. Johan Brandes' talk on the Emergence of Targeted Lung Cancer Therapy. The NetWork also wishes to highlight another upcoming scientific meeting of interest, The 14th World Congress on Lung Cancer, to be held July 2011, and the affiliated International Thymic Malignancies Interest Group (ITMIG).

Dr. Douglas Arenberg, FCCP
Chair, Thoracic Oncology

Transplant

Azithromycin in Lung Transplantation

Rates of chronic rejection following lung transplantation approach 45% at 5 years and reduce the 5-year survival to about 50%. The most common clinical surrogate of chronic rejection is bronchiolitis obliterans syndrome (BOS), which is defined as an irreversible loss in the FEV_1 of 20% or greater.

Currently, there are no satisfactory treatments for BOS. Following the success of erythromycin in diffuse panbronchiolitis, several groups have investigated the role of the neomacrolide azithromycin in treatment of BOS. Several retrospective and prospective studies have shown an improvement in the FEV_1, which is significant both clinically and statistically. In these reports, high BAL neutrophilia, typically greater than 15%, has been predictive of a response to azithromycin.

Two recent studies by the Belgian transplant group have looked at this in greater detail. The first study published in the *Journal of Heart and Lung Transplantation* in December 2010 (Vos et al. *J Heart Lung Transplant*. 2010; 29[12]:1358) was a retrospective look at long-term azithromycin therapy for BOS in 103 patients and showed an improvement in pulmonary function and survival in patients with BOS.

The second study by the same group that was published in the *European Respiratory Journal* (Vos et al. *Eur Respir J*. 2011;37[1]:164) was a randomized, prospective, placebo-controlled trial looking at the role of azithromycin in preventing BOS and showed a much lower incidence of BOS in patients treated with the drug.

The addition of azithromycin is the first intervention that has been shown to reverse the loss of lung function in patients with BOS and is a standard therapy for BOS, but with recent data, it should be considered upfront for the prevention of BOS.

Dr. Rajat Walia, FCCP
Steering Committee Member

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

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.

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(ceftaroline fosamil) for injection
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Introducing TEFLARO™

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.

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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

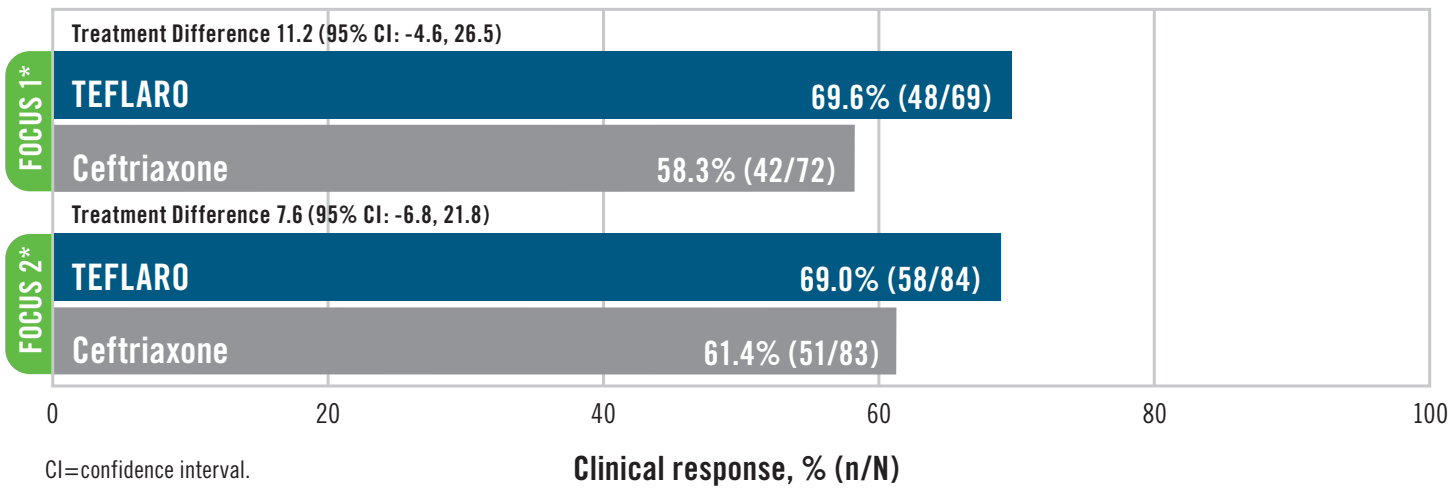
Adverse Reactions

- 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]



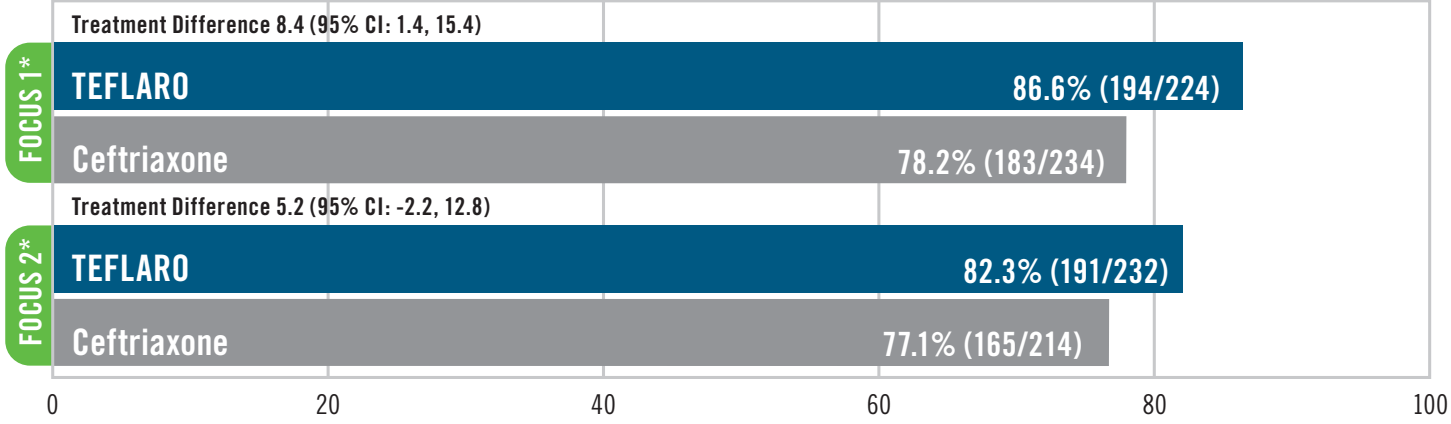
CI=confidence interval.

Clinical response, % (n/N)

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.

Clinical cure rates, % (n/N)

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.

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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.

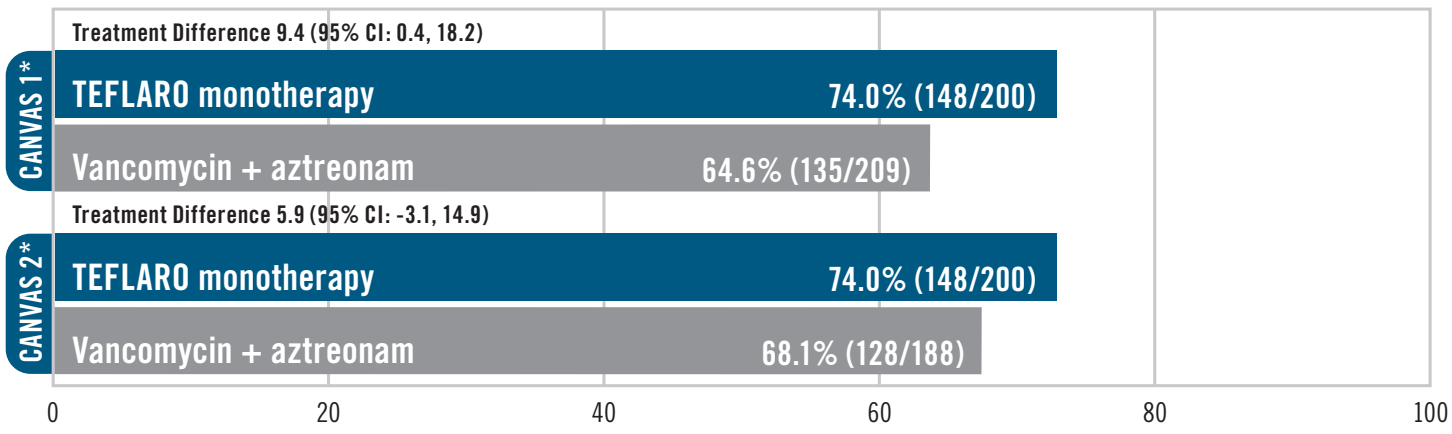
IMPORTANT SAFETY INFORMATION

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]

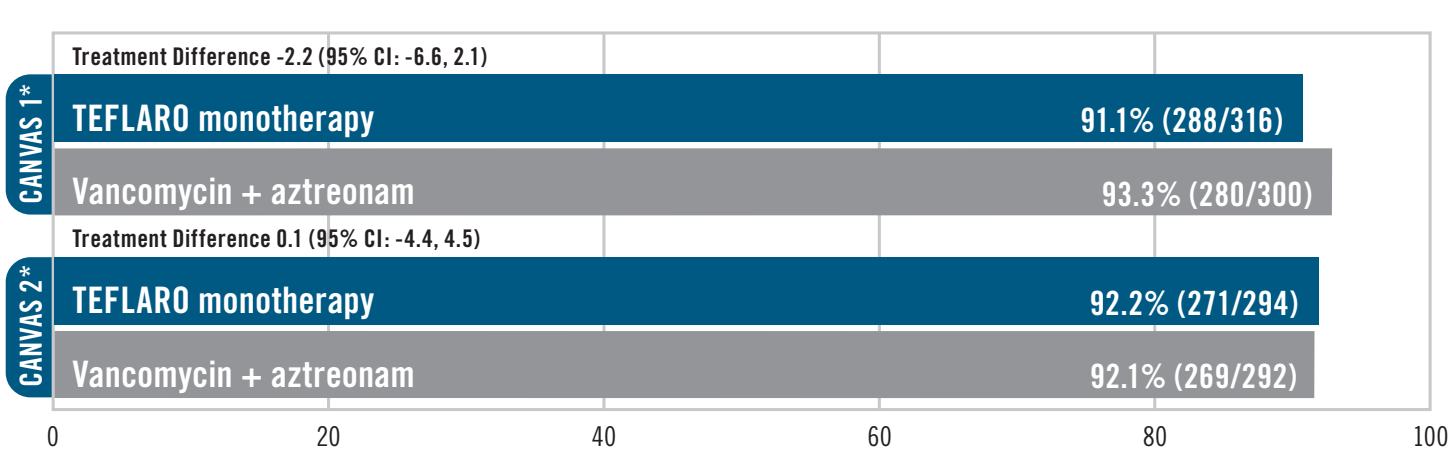


CI=confidence interval.

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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Apnea Likely Cause of Deaths

Bariatric • *from page 1*

Dr. Gallagher and his team measured carbon dioxide partial pressures transcutaneously ($Ptcco_2$) to gauge hypoventilation in 20 patients (14 female) during the first 24 hours after Roux-en-Y gastric bypass. Patients also wore blood oxygen saturation (Spo_2) ear-clip sensors.

Their mean body mass index was 54 kg/m^2, and 15 were diagnosed with OSA. All were on postoperative narcotics. As in the previous study, all the patients had multiple episodes of prolonged hypoxemia, with a mean of 191 episodes per patient lasting a mean of 1 minute.

Mean Spo_2 was 94%, and mean minimum Spo_2 was 60%. Patients spent about 5% of their time (75 minutes) with Spo_2 below 88%; hypoxemia lasted longer than 5 minutes in three patients.

All patients also had mild hypercarbia, suggesting mild, chronic hypoventilation. They had a mean $Ptcco_2$ of 44 mm Hg and a mean maximum of 56 mm Hg. The maximum $Ptcco_2$ value recorded in any patient was 75 mm Hg. Heart rates temporarily dropped below 50 bpm in 14 patients.

However, "in no patient could hypoxemia be explained entirely by hypoventilation, and there was no obvious relationship between hypoxemic episodes and [hypoventilation]," said Dr. Krista Haines, a recent University of South Florida graduate now with the University of Nevada, Las Vegas, who presented the findings at the annual Academic Surgical Congress.

The mild hypoventilation by itself was "not clinically significant," leaving obstructive sleep apnea as the most likely cause of hypoxemia following bariatric surgery, Dr. Gallagher stated.

As far as the unexplained deaths go, Dr. Gallagher and his team believe that once patients desaturate, the mild narcotic-induced hypoventilation pushes a few of them over the edge, though no one died in the study.

Because sleep apnea is the likely root cause of such deaths, Dr. Gallagher recommends routine postoperative monitoring of bariatric surgery patients. "[Apneics] need to have their CPAP on" after surgery, especially when receiving narcotics, he said.

CPAP and postoperative monitoring are necessary until sleep apnea resolves, usually after a weight loss of 50-75 pounds. In his study, he noted that 14 patients had machines but still desaturated. Barring faulty gear or incorrect settings, that means the machines weren't being used throughout the night.

He also pointed out the supplemental oxygen used in the study didn't prevent hypercarbia or hypoxemia and seems to have no therapeutic role at this point.

In many places, sleep apnea screens, CPAP, and nighttime pulse oximetry are not the standard of care following bariatric surgery, Dr. Gallagher said.

Dr. Stefan Holubar, a colorectal surgeon and comoderator of the session, thinks that needs to change.

"The standard of care should include formal obstructive sleep apnea [screening] for all patients undergoing bariatric surgery, or they should all be empirically treated [with CPAP] regardless of whether or not they have the diagnosis," said Dr. Holubar, of Dartmouth-Hitchcock Medical Center in Lebanon, N.H.

"Although it's a small pilot study, there are profound implications," he added.

Dr. Gallagher and his team are considering a randomized study to further investigate the issue, and they plan to include obese people having other kinds of operations.

Dr. Gallagher and Dr. Haines said they have no conflicts of interest. The study received no outside funding. ■

TEFLARO™ (ceftaroline fosamil) injection for intravenous (IV) use **Rx Only**
Brief Summary of Full Prescribing Information
Initial U.S. Approval: 2010

INDICATIONS AND USAGE: Teflaro™ (ceftaroline fosamil) is indicated for the treatment of patients with the following infections caused by susceptible isolates of the designated microorganisms. **Acute Bacterial Skin and Skin Structure Infections -** 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.* **Community-Acquired Bacterial Pneumonia -** 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.* **Usage -** 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. Appropriate specimens for microbiological examination should be obtained in order to isolate and identify the causative pathogens and to determine their susceptibility to ceftaroline. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

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.

WARNINGS AND PRECAUTIONS: Hypersensitivity Reactions - Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and serious skin reactions have been reported in patients receiving 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. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of *C. difficile. C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary 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. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated *[see Adverse Reactions].* **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. In the pooled Phase 3 CABP trials, 51/520 (9.8%) of Teflaro-treated patients compared to 24/534 (4.5%) of ceftriaxone-treated patients seroconverted from a negative to a positive direct Coombs' test result. 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. Diagnostic studies including a direct Coombs' test, should be performed. If drug-induced hemolytic anemia is suspected, discontinuation of Teflaro should be considered and supportive care should be administered to the patient (i.e. transfusion) 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.

ADVERSE REACTIONS: The following serious events are described in greater detail in the Warnings and Precautions section: Hypersensitivity reactions; *Clostridium difficile*-associated diarrhea; Direct Coombs' test seroconversion. **Adverse Reactions from Clinical Trials -** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be compared directly to rates from clinical trials of another drug and may not reflect rates observed in practice. Teflaro was evaluated in four controlled comparative Phase 3 clinical trials (two in ABSSSI and two in CABP) which included 1300 adult patients treated with Teflaro (600 mg administered by IV over 1 hour every 12h) and 1297 patients treated with comparator (vancomycin plus aztreonam or ceftriaxone) for a treatment period up to 21 days. The median age of patients treated with Teflaro was 54 years, ranging between 18 and 99 years old. Patients treated with Teflaro were predominantly male (63%) and Caucasian (82%). **Serious Adverse Events and Adverse Events Leading to Discontinuation -** 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. The most common SAEs in both the Teflaro and comparator treatment groups were in the respiratory and infection system organ classes (SOC). 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 comparator group. **Most Common Adverse Reactions -** 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. Table 4 in the full prescribing information lists adverse reactions occurring in ≥ 2% of patients receiving Teflaro in the pooled Phase 3 clinical trials (two in ABSSSI and two in CABP). The first value displays the percentage of patients in the pooled Teflaro trials (N=1300) and the second shows the percentage in the Pooled Comparators[a] trials (N=1297). **Gastrointestinal disorders:** Diarrhea (5%, 3%), Nausea (4%, 4%), Constipation (2%, 2%), Vomiting (2%, 2%); **Investigations:** Increased transaminases (2%, 3%); **Metabolism and nutrition disorders:** Hypokalemia (2%, 3%); **Skin and subcutaneous tissue disorders:** Rash (3%, 2%); **Vascular disorders:** Phlebitis (2%, 1%) [a] Comparators included vancomycin 1 gram IV every 12h plus aztreonam 1 gram IV every 12h in the Phase 3 ABSSSI trials, and ceftriaxone 1 gram IV every 24h in the Phase 3 CABP trials. **Other Adverse Reactions Observed During Clinical Trials of Teflaro -** Following is a list of additional adverse reactions reported by the 1740 patients who received Teflaro in any clinical trial with incidences less than 2%. Events are categorized by System Organ Class. **Blood and lymphatic system disorders -** Anemia, Eosinophilia, Neutropenia, Thrombocytopenia; **Cardiac disorders -** Bradycardia, Palpitations; **Gastrointestinal disorders -** Abdominal pain; **General disorders and administration site conditions -** Pyrexia; **Hepatobiliary disorders -** Hepatitis; **Immune system disorders -** Hypersensitivity, Anaphylaxis; **Infections and infestations -** *Clostridium difficile* colitis; **Metabolism and nutrition disorders -** Hyperglycemia, Hyperkalemia; **Nervous system disorders -** Dizziness, Convulsion; **Renal and urinary disorders -** Renal failure; **Skin and subcutaneous tissue disorders** - Urticaria.

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 *[see Clinical Pharmacology].*

USE IN SPECIFIC POPULATIONS: Pregnancy Category B - Developmental toxicity studies performed with ceftaroline fosamil in rats at IV doses up to 300 mg/kg demonstrated no maternal toxicity and no effects on the fetus. A separate toxicokinetic study showed that ceftaroline exposure in rats (based on AUC) at this dose level was approximately 8 times the exposure in humans given 600 mg every 12 hours. There were no drug-induced malformations in the offspring of rabbits given IV doses of 25, 50, and 100 mg/kg, despite maternal toxicity. Signs of maternal toxicity appeared secondary to the sensitivity of the rabbit gastrointestinal system to broad-spectrum antibacterials and included changes in fecal output in all groups and dose-related reductions in body weight gain and food consumption at ≥ 50 mg/kg; these were associated with an increase in spontaneous abortion at 50 and 100 mg/kg. The highest dose was also associated with maternal moribundity and mortality. An increased incidence of a common rabbit skeletal variation, angulated hyoid alae, was also observed at the maternally toxic doses of 50 and 100 mg/kg. A separate toxicokinetic study showed that ceftaroline exposure in rabbits (based on AUC) was approximately 0.8 times the exposure in humans given 600 mg every 12 hours at 25 mg/kg and 1.5 times the human exposure at 50 mg/kg. Ceftaroline fosamil did not affect the postnatal development or reproductive performance of the offspring of rats given IV doses up to 450 mg/kg/day. Results from a toxicokinetic study conducted in pregnant rats with doses up to 300 mg/kg suggest that exposure was ≥ 8 times the exposure in humans given 600 mg every 12 hours. There are no adequate and well-controlled trials in pregnant women. Teflaro should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers -** 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. **Pediatric Use -** Safety and effectiveness in pediatric patients have not been established. **Geriatric Use -** Of the 1300 patients treated with Teflaro in the Phase 3 ABSSSI and CABP trials, 397 (30.5%) were ≥ 65 years of age. The clinical cure rates in the Teflaro group (Clinically Evaluable [CE] Population) were similar in patients ≥ 65 years of age compared with patients < 65 years of age in both the ABSSSI and CABP trials. The adverse event profiles in patients ≥ 65 years of age and in patients < 65 years of age were similar. The percentage of patients in the Teflaro group who had at least one adverse event was 52.4% in patients ≥ 65 years of age and 42.8% in patients < 65 years of age for the two indications combined. Ceftaroline is excreted primarily by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in this age group and it may be useful to monitor renal function. Elderly subjects had greater ceftaroline exposure relative to non-elderly subjects when administered the same single dose of Teflaro. However, higher exposure in elderly subjects was mainly attributed to age-related changes in renal function. Dosage adjustment for elderly patients should be based on renal function *[see Dosage and Administration and Clinical Pharmacology].* **Patients with Renal Impairment -** 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 (ESRD – defined as CrCl < 15 mL/min), including patients on hemodialysis (HD) *[see Dosage and Administration and Clinical Pharmacology].*

OVERDOSAGE: In the event of overdose, Teflaro should be discontinued and general supportive treatment given. Ceftaroline can be removed by hemodialysis. In subjects with ESRD administered 400 mg of Teflaro, the mean total recovery of ceftaroline in the dialysate following a 4-hour hemodialysis session started 4 hours after dosing was 76.5 mg (21.6% of the dose). However, no information is available on the use of hemodialysis to treat overdosage *[see Clinical Pharmacology].*

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COMMENTARY

Dr. Paul Selecky, FCCP, comments: This is an important issue in the management of these patients. It is well established that the frequency and severity of obstructive sleep apnea (OSA) has a direct correlation with the severity of obesity. Their recommendation to make preoperative OSA evaluation and treatment of bariatric surgery patients a standard of care is well directed – the ounce of prevention versus the pound of care.

Private Practice Under Pressure From EHR Mandate

BY MITCHEL L. ZOLER
Elsevier Global Medical News

LAS VEGAS – The electronic health record mandate for physicians who participate in Medicare or Medicaid may have the unintended consequence of being the cudgel that drives many remaining private practice physicians out of business, Dr. Steve G. Peters, FCCP, said at the annual meeting of the National Association for Medical Direction of Respiratory Care.

"No one will admit it, but there is de facto pressure [from the electronic health record mandate] that there won't be private practice in the foreseeable future," said Dr. Peters, a critical care physician and professor of medicine at the Mayo Clinic in Rochester, Minn.

"Everyone will need to report measures on hundreds of patients," and to afford to do that they will likely have to become part of an organization, he predicted.

The challenge of meeting the electronic health record (EHR) reporting requirements will ratchet up over the next several years as the increasingly demanding stages of the Health Information Technology for Economic and Clinical Health (HITECH) Act begin to kick in.

In stage 1, which started this year, physicians using a certified EHR and participating in Medicare or Medicaid must report to the Center for Medicare and Medicaid Services (CMS) three core measures for each patient – height, weight, and blood pressure – as well as three additional measures from a list of 38 options. During the next few years, the program will expand into stages 2 and 3 with additional data reporting requirements.

"It sounds easy, but it's not," said Dr. Peters. The way to program an EHR to report these various measures "differs from measure to measure, and when you get into it, it's very complicated. We're [currently] working this through at Mayo. We have a full EHR at Mayo, but extracting out the data for reporting is proving to be difficult. We have 85% of it, but the gap, the final 15%, is hard."

As an example, he cited the challenge of automatically reporting to the CMS what happens with patients who have a body mass index of 30 kg/m^2 or greater. "You need to record and report an action plan of what you'll do about this, and if not, why not. You need to somehow capture it in a file that can be reported out of your computer why you did not achieve the measure."

The EHR information demands required by the HITECH law are "overwhelming," commented Dr. Alan H. Morris, FCCP, a pulmonologist and professor of medicine at the University of Utah in Salt Lake City. "It's a huge operation. What if a physician does not have the infrastructure of the Mayo Clinic?"

Those consequences were exemplified by an attendee at the meeting, Dr. Theodore S. Ingrassia III, FCCP, a pulmonologist in private practice who maintains an office cooperatively with two other pulmonologists in Rockford, Ill.

'There is de facto pressure [from the EHR mandate] that there won't be private practice in the foreseeable future.'

DR. PETERS

"The EHR is a disaster for us, because the cost of the hardware and software is just a fraction of the total cost. There is the expensive cost of getting an IT person to help maintain it and keep it current with all the demands. It may drive us out" of private practice, Dr. Ingrassia said during the session.

"Many predicted that the [$44,000] incentive from CMS will not buy much EHR for a big, complex practice. It is a sobering phenomenon," Dr. Peters said.

"The EHR is supposed to be a tool to help physicians organize their care, but it is being turned into something like an enemy," said Dr. Dennis E. Doherty, FCCP, a pulmonologist and critical care medicine physician and professor of medicine at the University of Kentucky in Lexington.

The three major hospitals in Rockford recognized the information technology and cost challenges that the new EHR requirements pose, and have offered to provide Dr. Ingrassia with the IT support he needs to meet CMS reporting demands if he gives up his private practice and joins their staff. It's a tempting proposal, he said, but he remains very reluctant to abandon the private practice he built over the past 20 years, he said in an interview.

For the time being, his strategy rests on deferring the EHR with the hope that the financial penalties scheduled to start in 2015 for noncompliance may get delayed or that some other option emerges.

Dr. Peters, Dr. Morris, Dr. Ingrassia, and Dr. Doherty had no disclosures relevant to this topic. ■

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Omalizumab Cuts Asthma Symptoms, Hospitalizations

BY MARY ANN MOON
Elsevier Global Medical News

Adding omalizumab to guideline-based asthma treatment decreased symptoms, exacerbations, hospitalizations, and the need for glucocorticoids in children, adolescents, and young adults living in the inner city, according to a recent report.

The monoclonal anti-IgE antibody was particularly effective in patients who were allergic to cockroach and dust allergens. Moreover, "a striking additional post hoc finding was the marked reduction in seasonal exacerbations seen with omalizumab," said Dr. William W. Busse of the University of Wisconsin, Madison, and his associates.

"Our purpose in designing this study was to examine whether specifically targeting the allergic component in persistent asthma would offer a benefit beyond that provided by conventional treatment for asthma control, regardless of disease severity," they noted.

The investigators compared subcutaneous injections of omalizumab vs. placebo injections in a multicenter clinical trial involving 419 children, adolescents, and young adults (aged 6-20 years) who had persistent allergic asthma. After 1 month on guideline-based treatment, the study participants were randomly assigned to additionally receive active (208 subjects) or placebo (211 subjects) injections every 2 weeks or 4 weeks, for a total of 60 weeks.

At baseline, the average number of days during the preceding 2 weeks in which participants had asthma symptoms was 4.9, and 25% of patients had been hospitalized at least once during the preceding year for an asthma-related event. The average age of the study subjects was 11 years. In all, 58% were male; 60% were black, and 37% were Hispanic.

The primary outcome (defined as the number of symptomatic days during the preceding 2 weeks) was decreased to 0.48 days with omalizumab, compared with 1.48 days with placebo, a significant 25% reduction. Exacerbations occurred in 49% of the placebo group, compared with 30% of the omalizumab group, which was also a significant difference. And the rate of asthma-related hospitalizations also was significantly lower with omalizumab (1.5%) than with placebo (6.3%).

Patients who took omalizumab were able to significantly reduce their use of inhaled glucocorticoids, with an overall budesonide-equivalent dose of 663 mcg/day, compared with 771 mcg/day with placebo.

These benefits "were similar in patients of all ages and at all levels of asthma severity," and were first observed within 4 weeks of beginning the injections, Dr. Busse and his colleagues said (N. Engl. J. Med. 2011;364:1005-15).

"No differences of concern regarding safety were noted between the two groups," they added.

The greatest treatment effect was seen in participants who were sensitized to cockroach allergen and were known to be exposed to it, based on environmental sampling from their bedrooms. These subjects had a 71% reduction in asthma exacerbations. Subjects who were allergic to dust mites also showed greater reductions in days with symptoms and the use of glucocorticoids, compared with those not sensitized to dust mites.

"Even though we found omalizumab effective at all levels of asthma severity, we do not advocate its use outside of current recommendations given its cost and remaining questions regarding long-term safety in children. We do, however, believe that this study provides a strong proof of concept that the allergic component of asthma is crucial in this population," the investigators said.

In a post hoc analysis, the researchers found that omalizumab also markedly reduced seasonal exacerbations of asthma. "Viral respiratory infections are a major cause of exacerbations, especially in the fall, with the start of school, but they were identified in less than 60% of the samples available for analysis, suggesting that other factors, such as allergen exposure, pollution, stress, or bacteria, also contribute to the risk of exacerbation.

These findings imply that targeting the drug to patients who are sensitized to cockroach and dust mite allergens, as well as focusing its use on preventing seasonal peaks in asthma exacerbations, would yield the optimal effectiveness and cost benefit, they added.

This study was supported by the National Institute of Allergy and Infectious Diseases, the National Center for Research Resources, and Novartis Pharmaceuticals. Dey Pharma provided EpiPens and S.C. Johnson provided household pest control products. Dr. Busse and his associates reported ties to numerous drug and device manufacturers. ■

COMMENTARY

Dr. Burt Lesnick, FCCP, comments: Omalizumab is not yet approved by the U.S. FDA for children under 12 years of age. In this study population, there were no adverse effects in children aged 6-12 years.

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AMERICAN COLLEGE OF CHEST PHYSICIANS
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Relieving Needless Suffering

Pediatric • *from page 1*

The care starts at diagnosis, continues through the trajectory of the illness, and is directed at the underlying illness and at the physical, emotional, social, and spiritual needs of the child and family.

More than 15,000 children and teens die in the United States each year from life-limiting diseases – and less than a quarter of them have cancer, according to data cited by Dr. Friedrichsdorf. Neuromuscular or neurodegenerative disorders cause a significant proportion of those deaths, followed by congenital or genetic disorders, cardiovascular disorders, and metabolic disorders.

"The vast majority of these children do not have access to pediatric palliative care in this country," Dr. Friedrichsdorf said in an interview. Data show that these children are suffering needlessly from pain, breathlessness, nausea, and vomiting.

Praised by the awards committee for "innovative symptom management, compassion, and family-centered care," Dr. Friedrichsdorf said he and his team take "an extremely aggressive approach" to managing pain and distressing symptoms in children with life-threatening or life-limiting conditions.

He believes strong pain medications are underused in children (and one of the "myths" he debunks is that increasing doses of opioids and/or benzodiazepines causes respiratory depression and quickens death), but also that pharmacology alone is insufficient.

His department employs both pharmacology and complementary therapies such as biofeedback, massage, hypnosis, acupuncture, and acupressure. Physicians and other staff are trained in such modalities. "It's not one or the other. It's using the whole breadth [of therapies] at the same moment," said Dr. Friedrichsdorf, who is trained in self-hypnosis.

"We want to promise each family, if your child is suffering from distressing symptoms like nausea, pain, or dyspnea, we can usually make these symptoms go away," he said. "Our goal is for children to live as long as possible, as well as possible."

In addition to physicians and nurses, the pain and palliative care team at Children's includes social workers, psychologists, a physical therapist, a child-life specialist, massage therapists, and advanced practice nurses.

Each of these professionals can see patients as part of a hospital-based pain and palliative care "rounding team" in the department's pain and palliative care clinic, or for patients in the Minneapolis/St. Paul area, in the home through the department's home-based component. The team can be called upon by anyone – a doctor, a patient, or a relative or friend – for a consultation, and its members meet regularly to discuss patients.

"My physical therapist may tell me, for instance, that I need to change [a patient's] pain medications because she sees side effects," Dr. Friedrichsdorf said.

A pilot study of pediatric palliative care teams at eight children's hospitals, to be published soon, found that professionals in the teams had a "clear idea of what the other professionals offered to the patient and family," said Nancy Berlinger, Ph.D., deputy director and research scholar at the Hastings Center, which conducted the study with researchers at Rush University, Chicago.

A chaplain knows, for instance, how the physician and nurse are addressing the patient's medical needs, and the physician is aware that the chaplain is supporting the parents and, in some cases, the child, she said in an interview.

"Having shared goals of care and strong communication is also important so that everything doesn't have to be explained every time a shift changes or a patient is transferred to a different setting," she said.

ONE GOAL IS TO 'INFLUENCE THE CULTURE OF HEALTH CARE SO THAT PEDIATRIC PALLIATIVE CARE IS RECOGNIZED AS ETHICALLY MANDATORY.'

"Most of these pediatric palliative care teams are fairly newly established," she noted. "There was some pediatric palliative care before then, but not necessarily with a strong team approach."

Dr. Nageswaran, who led the establishment of the first pediatric palliative care program at her hospital in 2008, said she was struck by the amount of coordination needed to provide good palliative care and by the flexibility needed to design a good program.

She and her colleagues started the program as a consult service for children who were hospitalized with complicated, often life-limiting conditions. The service used a half-time nurse coordinator, a one-quarter full-time equivalent (FTE) clinician post to be shared by a handful of physicians for rotating on-call duty, and a 1% FTE post for a physician coordinator.

"Very soon, we realized that the biggest need was to facilitate collaboration between multiple providers and to ensure sufficient continuity of care as these children transition back and forth from the hospital to home," Dr. Nageswaran said in an interview. "We weren't achieving this with the traditional consult model where we'd see patients in the hospital and leave recommendations for the primary medical team."

In a subsequent restructuring, physician time was consolidated into a one-third–time FTE coordinator post, which Dr. Nageswaran fills herself, and funding was obtained from the federal Maternal and Child Health Bureau to add another half-time nurse coordinator who could focus on making home visits and coordinating home-based care in one county.

The flexibility to coordinate care outside the hospital is critical, Dr. Nageswaran said. One of the 235 children cared for under the palliative care program thus far was a child with a rare genetic disorder characterized by skeletal abnormalities, urologic abnormalities, and severe neurologic impairment and seizures.

"The family wanted end-of-life care to be delivered at home, but they didn't want to forgo medical care," Dr. Nageswaran recalled. "We went step-by-step, aligning the family's wishes with the care the child received. We worked with the primary care doctor, the subspecialists, the home health agency, and the parents to provide medical treatment, pain and symptom management, and other care at home."

Both she and Dr. Friedrichsdorf emphasized the value of open inquiry with parents, children, and families.

"Each family is unique in how they perceive illness and how they make decisions about treatment and end-of-life care," said Dr. Nageswaran. "When we meet families, we meet them without a set agenda, and we make sure we don't impose our structure."

Similarly, Dr. Friedrichsdorf said, "When I enter a room, the first thing I say is, 'How can I help you?' We start with that open question." At that point, he said, surveys or other structured tools can be used to help determine needs and care plans.

One of the thorns in the field of pediatric palliative care is the unavailability of hospice services for many children, given the prognostic uncertainty of most childhood life-threatening conditions and the desire for continued treatment. Currently, most families have to forgo home-health services in order to receive hospice services.

Some states have taken action; policy reform passed in California in 2006, for instance, makes it easier for parents to utilize the Medi-Cal hospice benefit for children. A section of the federal Patient Protection and Affordable Care Act, moreover, is expected to change the Medicaid system to allow children with life-limiting conditions to receive both hospice care and curative treatment.

Another problem is poor provider reimbursement. "Physician services are reimbursed, but not enough to account for the amount of time involved," said Dr. Nageswaran. "And the services of nurses and social workers, who are key to pediatric palliative care programs, are not reimbursed."

She jump-started her program with a grant from the Duke Endowment, a private foundation, but now relies primarily on financial support from the hospital. Dr. Friedrichsdorf estimates that his hospital is reimbursed for only about half of its costs, and says that it relies heavily on philanthropy to make up the difference.

Philanthropy recently benefited the pediatric palliative care program at Akron (Ohio) Children's Hospital. With $1.2 million in donations from the Haslinger Family Foundation and other leadership gifts, the hospital has created an endowed chair for its services, which began in 2002.

One goal in the meantime, said Dr. Berlinger, is to "influence the culture of health care so that pediatric palliative care is recognized as ethically mandatory."

The $15,000 awards that Dr. Nageswaran and Dr. Friedrichsdorf received were given by the Hastings Center, a bioethics research institute based in Garrison, N.Y., in partnership with the Cunniff-Dixon Foundation, a foundation that focuses on the doctor-patient relationship near the end of life. ■

New Subspecialty Is Evolving

In terms of education, pediatric palliative care might be where pediatric subspecialties such as pulmonary care or neonatology were 25 years ago, Dr. Friedrichsdorf said, with an initial cadre of trained physicians having emerged.

In 2008, 47 physicians were certified in Hospice and Palliative Medicine (HPM) by the American Board of Pediatrics after taking the first American Board of Medical Specialties–recognized examination for the subspecialty. In total, 1,274 physicians were certified by various boards in the new subspecialty.

The American Board of Medical Specialties (ABMS) approved the creation of HPM as a subspecialty of 10 participating boards in 2006. Prior to 2006, board certification in hospice and palliative medicine was administered by the American Board of Hospice and Palliative Medicine but not recognized by the ABMS.

Other pediatricians have taken courses and attended educational retreats through organizations such as the Initiative for Pediatric Palliative Care, Dr. Berlinger said.

Ideally, she and Dr. Friedrichsdorf say, both educational tracks – fellowships and educational opportunities for mid-career physicians – will grow.

Starting in 2013, physicians who want to sit for the HPM board exam will have to have completed an Accreditation Council for Graduate Medical Education–accredited fellowship – a change that should spur the development of more fellowship programs. Children's Hospitals and Clinics of Minnesota, Dr. Friedrichsdorf's hospital, houses one of a handful of fellowship programs in pediatric palliative care. It has applied for ACGME approval.

Dr. Friedrichsdorf is the principal investigator of a National Institutes of Health/National Cancer Institute study on the creation and implementation of a pediatric palliative care curriculum that is slated to be offered to physicians who are in the midst of their careers and are not seeking subspecialty training.

"Many professionals working in children's hospitals are likely to care for a dying child, and need to be comfortable and knowledgeable," said Dr. Friedrichsdorf, who completed a fellowship in pediatric pain and palliative care at the Children's Hospital at Westmead, Australia, after finishing his pediatric residency in Germany.

CT Trial Said to Change Lung Ca Screening Landscape

BY MITCHEL L. ZOLER
Elsevier Global Medical News

LAS VEGAS – The results from the National Lung Screening Trial constitute a "game changer" for lung cancer screening, Dr. James R. Jett, FCCP, said at the annual meeting of the National Association for Medical Direction of Respiratory Care.

The study results, reported in a press release by the National Cancer Institute last November, "changed the landscape" for screening by showing that lung imaging by low-dose helical CT done annually for 3 years in people with a smoking history of at least 30 pack-years cut their lung cancer mortality during follow-up by 20%, compared with those who had three annual chest x-rays. "This is the biggest advance in lung cancer in my career, an absolutely stunning result," said Dr. Jett, a pulmonologist and lung cancer specialist at National Jewish Health in Denver.

The researchers who ran the National Lung Screening Trial will likely publish their full results this spring, after which annual screening of people who match the profile of those in the study should become the standard of care, Dr. Jett predicted.

The screening trial enrolled 53,454 current or former cigarette smokers aged 55-74 years, who had each accumulated at least 30 pack-years of smoking history but had quit within the previous 15 years. The more than 75,000 total screening events by CT and more than 73,000 total screens by chest x-ray yielded 24% positive CT images and 7% positive x-ray images. During roughly 144,000 person-years of follow-up in each arm, the mortality due to lung cancer reached 246 deaths per 100,000 person-years in the CT group and 308 deaths per 100,000 person-years in the x-ray group, a 20% absolute mortality reduction with CT screening that was statistically significant, and which led the trial's Data and Safety Monitoring Board to stop the study and release the results.

The people screened by CT also had a 7% reduction in all-cause mortality, compared with those screened by x-ray, also a statistically significant difference.

As about 160,000 Americans die from lung cancer annually, a 20% cut in mortality from low-dose helical CT screening could potentially save about 32,000 lives a year in the United States alone. "That's almost like eliminating all 40,000 breast cancer deaths each year," Dr. Jett said.

The results did not directly address the question of how long annual screening should continue. In the trial, screening stopped after three annual examinations because of limited financial resources, although despite that the study cost about $200 million, he said. But his review of the results identified no suggestion that in routine practice screening should stop after 3 years. "There was no drop in the number of cancers" during each sequential year of screening. "I don't see anything that tells me you can stop [screening] after 3 years," he said.

"The biggest question is, can we afford" to do annual CT screening on the scale needed to include all people who fit the profile included in the trial.

A second issue is the safety of annual CT imaging, but Dr. Jett presented a brief analysis suggesting that it is safe. A low-dose CT scan involves a radiation exposure of about 0.65 mSv, less than 10% of the dose of a conventional chest CT, Dr. Jett said. With that level of exposure, annual low-dose CT imaging of currently smoking women aged 50 might cause an excess of 5 cancer deaths for every 10,000 people screened, compared with a background lung cancer mortality of 100 for every 10,000 people with no screening. Because screening could prevent 20% of these 100 deaths, it would avert more deaths that it might cause. For men, the risk: benefit ratio runs even higher because currently smoking men undergoing annual CT screening would have about 2 extra lung cancer deaths per 10,000 people due to the radiation exposure, compared with 110 per 10,000 without screening. Women face a higher risk from the radiation of screening than men because of the impact of chest radiation on breast cancer, Dr. Jett said.

Dr. Jett said that he has been an adviser to Genentech, Pfizer, and Bristol-Myers Squibb, and that he has a research grant pending from Oncimmune. ■

COMMENTARY

Dr. W. Michael Alberts, FCCP, comments: The news was eagerly anticipated and extremely well received. In November 2010, the Data and Safety Monitoring Board of the National Lung Screening Trial stopped the study and released the results. It appears that annual screening low-dose CT scans can save lives when compared with annual chest x-rays in a defined patient population over a defined period of time. This mortality benefit was the missing piece of information. Since screening for lung cancer is not without risk (cost, false positives, anxiety, and radiation exposure), it had been difficult to recommend screening without knowing if a mortality benefit could be anticipated.

Even with the positive NLST results, however, a blanket recommendation for annual CT screening is not currently prudent. The NLST study involved a specific population and therefore may not be applicable to all. Fortunately, help is on the way. A multisociety task force has been formed and is poised to review the full study results when available. The plan is to then rapidly formulate and publish guidelines for lung cancer screening. Additionally, the third edition of the ACCP's Evidence-based Guidelines on the Diagnosis and Management of Lung Cancer is being prepared. The new "Screening for Lung Cancer" chapter will be helpful to front-line clinicians. So, encourage your patients to stop smoking and look for guidelines in the near future.

Data Suggest Preop Smoking Cessation Not Harmful

BY MARY ANN MOON
Elsevier Global Medical News

Patients who quit smoking shortly before undergoing surgery are not at increased risk of postoperative complications, compared with those who continue to smoke, according to a report published online in the Archives of Internal Medicine.

"Until some new evidence of harm emerges, firm advice to stop smoking and an offer of smoking cessation treatment to those who need it can be provided to presurgical patients at any time," said Katie Myers of Queen Mary, University of London and her associates.

Publication of a study in 1989 with 39 subjects suggested that "stopping smoking leads to a decrease in coughing and an increase in sputum production." Although that article did not actually show a significant effect of smoking cessation on postoperative complications, it has continued to influence routine practice; in fact, some treatment guidelines recommend against smoking cessation in the 2 months prior to surgery "to minimize the increase in pulmonary complications in recent quitters."

Ms. Myers and her colleagues reviewed the literature for all studies that allowed comparisons of postoperative complications in patients who stopped smoking 8 weeks or less before undergoing surgery (recent quitters) and patients who continued to smoke. They then performed a meta-analysis of the nine studies that did so, rating as "high quality" the three studies that also used biochemical testing to validate subjects' self-report of their smoking status.

These studies involved 889 subjects, including 448 recent quitters and 441 continuing smokers.

Only one of the nine studies showed a significant effect of smoking cessation, and that was in favor of recent quitting. When the results were pooled, there was "no beneficial or detrimental effect of quitting within 8 weeks before surgery compared with continued smoking," the researchers said.

The results were the same in an analysis of the three high-quality studies, and likewise when the analysis was restricted to only pulmonary postoperative complications.

"In conclusion, there is currently no suggestion, either from any single study or from combinations of studies, that quitting smoking shortly before surgery increases postoperative complications," the investigators said (Arch. Intern. Med. 2011 [doi:10.1001/archinternmed.2011.97]).

The reluctance to allow or encourage smoking cessation shortly before surgery is based on unconfirmed assumptions. Only one study in the literature has directly examined mucociliary clearance in surgical patients shortly after smoking cessation, and that study found no significant difference between surgical patients who had recently quit and those who continued to smoke, Ms. Myers and her associates noted.

"No data are available on the effects of only a few days' abstinence from smoking. Early abstinence generates more intense withdrawal discomfort, but there is no clear rationale to expect this to translate into postoperative complications," they added.

However, they acknowledged that their study is limited by its observational nature and by the small number of studies available for review that have evaluated this issue. "Our findings are necessarily tentative and may be modified when more data become available," the researchers said. ■

VITALS

Major Finding: There is no evidence that stopping smoking shortly before undergoing surgery causes either benefit or detriment, compared with continuing to smoke.

Data Source: A meta-analysis of nine studies examining postoperative complications in 889 patients who either continued to smoke or stopped smoking 8 weeks or less before undergoing surgery.

Disclosures: One of Ms. Myers' associates is supported by the U.K. Center for Tobacco Control Studies. Two associates reported ties to GlaxoSmithKline, Novartis, Pfizer Global, and Johnson & Johnson, which manufacture smoking cessation products.

COMMENTARY

Dr. Richard Fischel, FCCP, comments: The authors performed a much-needed meta-analysis of existing data and have finally shown that there does not appear to be a detriment to patient health or postop recovery from smoking cessation prior to lung surgery. Although limited by its observational nature, the results are encouraging and I believe this should allow doctors to feel comfortable recommending smoking cessation prior to surgery.

COMMENTARY

IVC Filters Still Have a Role for Some Patients

There is much debate over certain aspects of the prevention and treatment of venous thromboembolism. However, most physicians agree that pulmonary embolism (PE) is a serious and potentially fatal condition, with approximately 300,000 patient deaths nationwide each year. Most of these deaths occur in hospitalized patients, and PE is considered to be the leading cause of preventable in-hospital mortality in the United States.

LUIS ANGEL, M.D.

More than 12 million patients admitted to hospitals across the country are known to be at high risk of pulmonary embolism and need prophylaxis (Am. J. Hematol. 2007;82:777-82).

The most recommended therapy, based on the ACCP guidelines, is the use of heparin or low-molecular-weight heparin as prophylactic anticoagulation (Chest 2008;133:454S-545S). An overwhelming number of patients receive this kind of therapy.

According to the guidelines, the use of filters is listed as an alternative for patients who are critically ill, are at high risk for pulmonary embolism, or have a contraindication to anticoagulation. These patients represent the minority of patients with VTE, but they are still in need of effective prophylactic therapy.

Anticoagulation has been shown to be a very safe therapy in most patients; however, for those patients who can't have anticoagulation, inferior vena cava (IVC) filters are an effective alternative for preventing pulmonary embolism.

The incidence of PE in patients who have vena cava filters in multiple clinical trials is about 1.3%, which is similar to the incidence reported in the PREPIC (Prevention of Recurrent Pulmonary Embolism by Vena Cava Interruption) study, a trial that randomized patients to anticoagulation plus a vena cava filter or to anticoagulation alone. In this study, the rates of PE during the first 12 days in patients with filters was 1.1%, and lower than in patients receiving anticoagulation alone (N. Engl. J. Med. 1998;338:409-16).

The research on IVC filters has not kept pace with the increasing clinical application of these devices. Why is there is no randomized, clinical trial studying the use of filters?

In my opinion, it is because trials are extremely complicated to do in this population of patients. These are patients who have a high risk of venous thromboembolism, who already have a VTE or pulmonary embolism, and who can't safely receive anticoagulation for many reasons, such as multiple trauma with bleeding, multiple operations, or intracerebral hemorrhage.

These patients are at high risk for developing a PE and something must be done for them. If we can't give anticoagulation, we can protect them with the use of IVC filters.

Only about 250,000 of the 12 million at-risk patients are receiving vena cava filters, and complications, even if considered severe, occur in fewer than 3% of the patients who receive filters as prophylaxis. The complications from vena cava filters are related to the period of time for which we use these devices, with few reported complications during the first 30 days of use. In some cases, the filters are used for a short period of time and are removed when the patient can go on anticoagulation therapy, or when he or she no longer has significant risk of VTE.

In my opinion, the IVC filters are effective for preventing a pulmonary embolism and are safe for most of these high-risk patients.

In conclusion, the significant alarm about filter use is mostly related to the long-term complications and the lack of randomized studies evaluating their effectiveness. Although these devices are complicated, that is not to say that they are not useful in a select group of patients, most of whom are in critical care or have contraindications to anticoagulation therapy.

If we monitor these patients closely, follow them with prophylactic anticoagulation, and improve the rates of IVC filter retrieval, we can balance the risk-benefit profile of these devices, and they will continue to be considered a good alternative for high-risk patients. ■

DR. ANGEL *is the director of the lung transplantation program in the department of medicine and CT surgery at the University of Texas Health Science Center in San Antonio, and works with a company developing products for critically ill patients, including a vena cava filter.*

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SIR, ACCP Vena Cava Filter Guidelines Diverge

BY MITCHEL L. ZOLER
Elsevier Global Medical News

MIAMI BEACH – Two major U.S. medical societies don't agree on which patients need an inferior vena cava filter.

The current, published guidelines of the American College of Chest Physicians (ACCP) and the Society of Interventional Radiology (SIR) lack agreement on the indications for placement of inferior vena cava filters during routine practice. And the implications of the contradictory guidelines are growing because use of inferior vena cava filters has risen significantly in recent years, Dr. Amanjit S. Baadh and his associates said in a poster they presented at ISET 2011, an international symposium on endovascular therapy.

Their analysis of 187 of these filters placed by interventional radiologists working at Lenox Hill Hospital in New York during January 2008–April 2010 showed that the hospital staff ordered 106 filters (57%) for indications not approved by the ACCP guidelines (Chest 2008;133:71S-109S) and 39 filters (21%) not in compliance with the SIR guidelines (J. Vasc. Interv. Radiol. 2006;17:449-59), reported Dr. Baadh, a physician at Lenox Hill, and his associates in the hospital's department of medicine. The review showed that 36% of the placed filters met SIR criteria for appropriate placement but failed to fall within an indication sanctioned by the ACCP.

The findings "highlight a wide disparity in national guidelines," and they "suggest a need for standardization of current guidelines espoused by professional societies," the researchers said in their poster.

Most of the filter placements that met the SIR guidelines but fell outside of the indications approved by the ACCP were done in patients judged to have fall risks, patients who had failed anticoagulation management or were noncompliant with anticoagulation medications, and patients with limited cardiopulmonary reserve.

Dr. Baadh and his associates reviewed 443 inferior vena cava filters placed at their hospital during the study period. They excluded 230 of these cases because the filters had not been placed by a member of the interventional radiology staff. They excluded another 26 cases because of incomplete patient records. The patients who received the 187 filters included in the analysis had an average age of 75 years, and 56% were women.

The analysis also showed a statistically significant link between which hospital service initiated the order for filter placement and compliance with the indication guidelines. About three-quarters of the patients who received filters included in the analysis were in a ward served by the internal medicine department or one of its subspecialties, and these patients received 87% of the 187 filters included in the analysis. The filters ordered by physicians from medicine or a medicine subspecialty met the SIR guideline criteria in 84% of cases and met the ACCP criteria in 46% of cases. In contrast, the smaller number of patients who received filters ordered by physicians not from medicine or a subspecialty met the SIR criteria in 46% of cases and met the ACCP criteria in 25% of cases.

Dr. Baadh said that he had no disclosures. ■

COMMENTARY

Dr. Victor Test, FCCP, comments: This retrospective study provides an interesting view on the use of inferior vena cava filters and the clinical practice guidelines that are currently published by the American College of Chest Physicians and the Society of Interventional Radiology. The study is retrospective and includes only those IVC filters placed by interventional radiology during the time period at that hospital. The study does not report any outcome data but reports a functional disparity between the SIR guidelines and the ACCP guidelines. Dr. Baadh reports that a higher percentage of filters placed that were not in compliance with ACCP guidelines than the SIR guidelines. The crucial difference between the guidelines is that the SIR guidelines include several relative indications, which accounted for over 20% of the patients who met the SIR guidelines. At least one of these relative indications might be interpreted as a contraindication to anticoagulation, so it allows some degree of interpretation that might have brought the percentage of patients who met both SIR and ACCP guidelines closer. The author suggests that differences between guidelines may be confusing for providers regarding treatment strategies, and it illustrates the difficulties that face health care providers, insurance companies, and hospitals who use these guidelines.

DR. TEST *is a steering committee member of the ACCP Pulmonary Vascular Disease NetWork.*

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Survey Sheds Light on Vena Cava Filter Practices

BY DOUG BRUNK
Elsevier Global Medical News

SAN DIEGO – In the hands of experienced vascular surgeons, the use of retrievable inferior vena cava filters was less common than with other specialists, except in trauma or bariatric cases, and superior vena cava filter placement was very rare.

Vena cava filter (VCF) "use has skyrocketed over the past 20 years with percutaneous insertion, low-profile retrievable devices, relative and prophylactic indications, and other interventionalists now placing filters," Dr. Mark Friedell said at the annual meeting of the American Venous Forum.

However, in August 2010 the Food and Drug Administration said it had received 921 reports of adverse events with inferior vena cava (IVC) filters since 2005, and recommended that patients be referred for removal of retrievable filters when feasible and clinically indicated.

Dr. Friedell, director of surgical education for Orlando Health, and his associate, Dr. Peter Nelson, assistant professor of vascular surgery at the University of Florida, Gainesville, sent a 17-question survey about VCF practices to all 276 members of the Southern Association for Vascular Surgery, an organization composed exclusively of board-certified vascular surgeons. Of the 276 members, 126 responded, for a response rate of 46%.

When asked about the IVC, respondents cited the Greenfield filter as their preferred permanent device (31%), followed by a variety of retrievable devices. Half of the respondents said that they rarely placed retrievable filters, 26% said that they placed them selectively, and 24% said that they usually placed them. They cited the Bard as their preferred retrievable filter (45%).

Despite the fact that 52% and 46% of respondents placed VCFs in trauma and bariatric patients, respectively, filters were placed for prophylactic indications less than 50% of the time by 63% of respondents.

Continued on following page

Remove IVC Filters Promptly to Avoid Complications

BY M. ALEXANDER OTTO
Elsevier Global Medical News

HUNTINGTON BEACH, CALIF. – Retrievable inferior vena cava filters should be removed once the acute risk of pulmonary embolism or deep vein thrombosis has passed, instead of being left in patients indefinitely, according to Dr. John Curci, a vascular surgeon at Washington University, St. Louis.

Despite the dearth of data about long-term risks, there are reports of filters thrombosing, migrating, fragmenting, and embolizing, with severe complications. Use of the filters has grown in recent years, and currently in U.S. patients, only about half of them are removed when no longer needed, he said (J. Hosp. Med. 2009;4:441-8).

"Should you remove the filters? I think just based on the fact that we don't have good long-term data, the answer is yes," he said, noting that filter removal is "fast, easy, and billable," with potentially an 85% or better retrieval rate.

'That's not minor, to have a piece of your filter in your heart.'

DR. CURCI

About 60 embolizations to the heart have been reported over the past 15 years. Such reports "need to be scaring us all a little bit until we really know what [the risks] are," Dr. Curci said (J. Invasive Cardiol. 2009;21:606-10).

Early in their development, the filters were placed therapeutically in patients with pulmonary embolisms (PEs) or deep vein thromboses (DVTs) or histories of them. With the development of retrievable filters, there has been a shift over the past 15 years to prophylactic placement when the risk of PE or DVT is anticipated to be high, or when there is a risk of bleeding with anticoagulation.

"This has led to a lot of excitement about putting these filters in, and so we are increasing [their] use," Dr. Curci said at the annual Academic Surgical Congress. However, the risk of fatal or debilitating PEs or DVTs in the absence of any preceding symptoms is low and usually short lived. Because of that low risk, the safety bar must be correspondingly high for filters meant to prevent PEs or DVTs, he said.

It is in that context that rare reports of filter fractures and embolisms become important. In one of the few attempts to assess long-term risk, 80 patients with filters placed between April 2004 and January 2009 underwent fluoroscopy to assess filter integrity. Filters had fractured and fragmented in 13 patients and embolized in 7, including 5 patients with embolization to the heart. Three of those five patients experienced life-threatening ventricular tachycardia and/or tamponade. One patient died (Arch. Intern. Med. 2010;170:1827-31).

"That's not minor, to have a piece of your filter in your heart. We have to think about [filter risks] not only in the short term, but also in the long term" and "whether placement is justified" in the first place, Dr. Curci said.

He said that he has no financial disclosures. ■

Continued from previous page

When asked how often they removed retrievable filters, 64% estimated that they did so less than 25% of the time and 78% estimated that they did so less than 50% of the time.

There were few major complications, including one case of atrial perforation and one case of migration to the heart. There were also 12 cases of IVC thrombosis (4 with TrapEase filters), 3 cases of strut emboli (all Bard filters), and 9 cases of severe tilting (eight Bard filters).

Until more experience is accrued with retrievable devices – particularly since the removal rate is low – he said that "they should not be used as permanent filters, and they should be removed as soon as possible. Ideally, filters should be placed by those who can provide complete care to the VTE patient, including the management of anticoagulation."

Dr. Friedell said that he had no relevant financial disclosures. ■

TYGACIL® (tigecycline) Brief Summary
See package insert for full Prescribing Information. For further product information and current package insert, please visit www.wyeth.com or call our medical communications department toll-free at 1-800-934-5556.
INDICATIONS AND USAGE
TYGACIL is indicated for the treatment of adults with complicated skin and skin structure infections caused by *Escherichia coli, Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus agalactiae, Streptococcus anginosus* grp. (includes *S. anginosus, S. intermedius,* and *S. constellatus*), *Streptococcus pyogenes, Enterobacter cloacae, Klebsiella pneumoniae,* and *Bacteroides fragilis.*
TYGACIL is indicated for the treatment of adults with complicated intra-abdominal infections caused by *Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus anginosus* grp. (includes *S. anginosus, S. intermedius,* and *S. constellatus*), *Bacteroides fragilis, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides vulgatus, Clostridium perfringens,* and *Peptostreptococcus micros.*
TYGACIL is indicated for the treatment of adults with community-acquired pneumonia infections caused by *Streptococcus pneumoniae* (penicillin-susceptible isolates), including cases with concurrent bacteremia, *Haemophilus influenzae* (beta-lactamase negative isolates), and *Legionella pneumophila.*
CONTRAINDICATIONS
TYGACIL is contraindicated for use in patients who have known hypersensitivity to tigecycline.
WARNINGS AND PRECAUTIONS
Anaphylaxis/Anaphylactoid Reactions
Anaphylaxis/anaphylactoid reactions have been reported with nearly all antibacterial agents, including TYGACIL, and may be life-threatening. TYGACIL is structurally similar to tetracycline-class antibiotics and should be administered with caution in patients with known hypersensitivity to tetracycline-class antibiotics.
Hepatic Effects
Increases in total bilirubin concentration, prothrombin time and transaminases have been seen in patients treated with tigecycline. Isolated cases of significant hepatic dysfunction and hepatic failure have been reported in patients being treated with tigecycline. Some of these patients were receiving multiple concomitant medications. Patients who develop abnormal liver function tests during tigecycline therapy should be monitored for evidence of worsening hepatic function and evaluated for risk/benefit of continuing tigecycline therapy. Adverse events may occur after the drug has been discontinued.
Mortality Imbalance and Lower Cure Rates in Ventilator-Associated Pneumonia
A study of patients with hospital acquired pneumonia failed to demonstrate the efficacy of TYGACIL. In this study, patients were randomized to receive TYGACIL (100 mg initially, then 50 mg every 12 hours) or a comparator. In addition, patients were allowed to receive specified adjunctive therapies. The sub-group of patients with ventilator-associated pneumonia who received TYGACIL had lower cure rates (47.9% versus 70.1% for the clinically evaluable population) and greater mortality (25/131 [19.1%] versus 14/122 [11.5%]) than the comparator.
Use During Pregnancy
TYGACIL may cause fetal harm when administered to a pregnant woman. If the patient becomes pregnant while taking tigecycline, the patient should be apprised of the potential hazard to the fetus. Results of animal studies indicate that tigecycline crosses the placenta and is found in fetal tissues. Decreased fetal weights in rats and rabbits (with associated delays in ossification) and fetal loss in rabbits have been observed with tigecycline [see **USE IN SPECIFIC POPULATIONS**].
Tooth Development
The use of TYGACIL during tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). Results of studies in rats with TYGACIL have shown bone discoloration. TYGACIL should not be used during tooth development unless other drugs are not likely to be effective or are contraindicated.
***Clostridium difficile*-Associated Diarrhea**
Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including TYGACIL, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*. *C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.
Patients With Intestinal Perforation
Caution should be exercised when considering TYGACIL monotherapy in patients with complicated intra-abdominal infections (cIAI) secondary to clinically apparent intestinal perforation. In cIAI studies (n=1642), 6 patients treated with TYGACIL and 2 patients treated with imipenem/cilastatin presented with intestinal perforations and developed sepsis/septic shock. The 6 patients treated with TYGACIL had higher APACHE II scores (median = 13) versus the 2 patients treated with imipenem/cilastatin (APACHE II scores = 4 and 6). Due to differences in baseline APACHE II scores between treatment groups and small overall numbers, the relationship of this outcome to treatment cannot be established.
Tetracycline-Class Effects
TYGACIL is structurally similar to tetracycline-class antibiotics and may have similar adverse effects. Such effects may include: photosensitivity, pseudotumor cerebri, and anti-anabolic action (which has led to increased BUN, azotemia, acidosis, and hyperphosphatemia). As with tetracyclines, pancreatitis has been reported with the use of TYGACIL.
Superinfection
As with other antibacterial drugs, use of TYGACIL may result in overgrowth of non-susceptible organisms, including fungi. Patients should be carefully monitored during therapy. If superinfection occurs, appropriate measures should be taken.
Development of Drug-Resistant Bacteria
Prescribing TYGACIL in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.
ADVERSE REACTIONS
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
In clinical trials, 2514 patients were treated with TYGACIL. TYGACIL was discontinued due to adverse reactions in 7% of patients compared to 6% for all comparators. Table 1 shows the incidence of treatment-emergent adverse reactions through test of cure reported in ≥2% of patients in these trials.

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

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

[a] Vancomycin/Aztreonam, Imipenem/Cilastatin, Levofloxacin, Linezolid.
[b] LFT abnormalities in TYGACIL-treated patients were reported more frequently in the post therapy period than those in comparator-treated patients, which occurred more often on therapy.
In all Phase 3 and 4 studies that included a comparator, death occurred in 3.9% (147/3788) of patients receiving TYGACIL and 2.9% (105/3646) of patients receiving comparator drugs. **An increase in all-cause mortality has been observed across phase 3 and 4 clinical studies in TYGACIL treated patients versus comparator. The cause of this increase has not been established. This increase should be considered when selecting among treatment options.** (See Table 2.)

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

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

CAP = Community-acquired pneumonia; cIAI = Complicated intra-abdominal infections; cSSSI = Complicated skin and skin structure infections; HAP = Hospital-acquired pneumonia; VAP = Ventilator-associated pneumonia; RP = Resistant pathogens; DFI = Diabetic foot infections.
* The difference between the percentage of patients who died in TYGACIL and comparator treatment groups.
[a] These are subgroups of the HAP population.
Note: The studies include 300, 305, 900 (cSSSI), 301, 306, 315, 316, 400 (cIAI), 308 and 313 (CAP), 311 (HAP), 307 [Resistant gram-positive pathogen study in patients with MRSA or Vancomycin-Resistant Enterococcus (VRE)], and 319 (DFI with and without osteomyelitis).
In comparative clinical studies, infection-related serious adverse events were more frequently reported for subjects treated with TYGACIL (7%) versus comparators (6%). Serious adverse events of sepsis/septic shock were more frequently reported for subjects treated with TYGACIL (2%) versus comparators (1%). Due to baseline differences between treatment groups in this subset of patients, the relationship of this outcome to treatment cannot be established [see **WARNINGS AND PRECAUTIONS**].
The most common treatment-emergent adverse reactions were nausea and vomiting which generally occurred during the first 1 – 2 days of therapy. The majority of cases of nausea and vomiting associated with TYGACIL and comparators were either mild or moderate in severity. In patients treated with TYGACIL, nausea incidence was 26% (17% mild, 8% moderate, 1% severe) and vomiting incidence was 18% (11% mild, 6% moderate, 1% severe).
In patients treated for complicated skin and skin structure infections (cSSSI), nausea incidence was 35% for TYGACIL and 9% for vancomycin/aztreonam; vomiting incidence was 20% for TYGACIL and 4% for vancomycin/aztreonam. In patients treated for complicated intra-abdominal infections (cIAI), nausea incidence was 25% for TYGACIL and 21% for imipenem/cilastatin; vomiting incidence was 20% for TYGACIL and 15% for imipenem/cilastatin. In patients treated for community-acquired bacterial pneumonia (CABP), nausea incidence was 24% for TYGACIL and 8% for levofloxacin; vomiting incidence was 16% for TYGACIL and 6% for levofloxacin.
Discontinuation from tigecycline was most frequently associated with nausea (1%) and vomiting (1%).
For comparators, discontinuation was most frequently associated with nausea (<1%).
The following adverse reactions were reported infrequently (<2%) in patients receiving TYGACIL in clinical studies:
Body as a Whole: injection site inflammation, injection site pain, injection site reaction, septic shock, allergic reaction, chills, injection site edema, injection site phlebitis
Cardiovascular System: thrombophlebitis
Digestive System: anorexia, jaundice, abnormal stools
Metabolic/Nutritional System: increased creatinine, hypocalcemia, hypoglycemia, hyponatremia
Special Senses: taste perversion
Hemic and Lymphatic System: partial thromboplastin time (aPTT), prolonged prothrombin time (PT), eosinophilia, increased international normalized ratio (INR), thrombocytopenia
Skin and Appendages: pruritus
Urogenital System: vaginal moniliasis, vaginitis, leukorrhea
Post-Marketing Experience
The following adverse reactions have been identified during postapproval use of TYGACIL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish causal relationship to drug exposure. Anaphylaxis/anaphylactoid reactions, acute pancreatitis, hepatic cholestasis, and jaundice.
DRUG INTERACTIONS
Warfarin
Prothrombin time or other suitable anticoagulation test should be monitored if tigecycline is administered with warfarin [see **CLINICAL PHARMACOLOGY (12.3)** in full Prescribing Information].
Oral Contraceptives
Concurrent use of antibacterial drugs with oral contraceptives may render oral contraceptives less effective.
USE IN SPECIFIC POPULATIONS
Pregnancy
Teratogenic Effects—Pregnancy Category D [see **WARNINGS AND PRECAUTIONS**]
Tigecycline was not teratogenic in the rat or rabbit. In preclinical safety studies, ^{14}C-labeled tigecycline crossed the placenta and was found in fetal tissues, including fetal bony structures. The administration of tigecycline was associated with slight reductions in fetal weights and an increased incidence of minor skeletal anomalies (delays in bone ossification) at exposures of 5 times and 1 times the human daily dose based on AUC in rats and rabbits, respectively (28 mcg·hr/mL and 6 mcg·hr/mL at 12 and 4 mg/kg/day). An increased incidence of fetal loss was observed at maternotoxic doses in the rabbits with exposure equivalent to human dose.
There are no adequate and well-controlled studies of tigecycline in pregnant women. TYGACIL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nursing Mothers
Results from animal studies using ^{14}C-labeled tigecycline indicate that tigecycline is excreted readily via the milk of lactating rats. Consistent with the limited oral bioavailability of tigecycline, there is little or no systemic exposure to tigecycline in nursing pups as a result of exposure via maternal milk.
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TYGACIL is administered to a nursing woman [see **WARNINGS AND PRECAUTIONS**].
Pediatric Use
Safety and effectiveness in pediatric patients below the age of 18 years have not been established. Because of effects on tooth development, use in patients under 8 years of age is not recommended [see **WARNINGS AND PRECAUTIONS**].
Geriatric Use
Of the total number of subjects who received TYGACIL in Phase 3 clinical studies (n=2514), 664 were 65 and over, while 288 were 75 and over. No unexpected overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity to adverse events of some older individuals cannot be ruled out.
No significant difference in tigecycline exposure was observed between healthy elderly subjects and younger subjects following a single 100 mg dose of tigecycline [see **CLINICAL PHARMACOLOGY (12.3)** in full Prescribing Information].
Hepatic Impairment
No dosage adjustment is warranted in patients with mild to moderate hepatic impairment (Child Pugh A and Child Pugh B). In patients with severe hepatic impairment (Child Pugh C), the initial dose of tigecycline should be 100 mg followed by a reduced maintenance dose of 25 mg every 12 hours. Patients with severe hepatic impairment (Child Pugh C) should be treated with caution and monitored for treatment response [see **CLINICAL PHARMACOLOGY (12.3)** and **DOSAGE AND ADMINISTRATION (2.2)** in full Prescribing Information].
OVERDOSAGE
No specific information is available on the treatment of overdosage with tigecycline. Intravenous administration of TYGACIL at a single dose of 300 mg over 60 minutes in healthy volunteers resulted in an increased incidence of nausea and vomiting. In single-dose intravenous toxicity studies conducted with tigecycline in mice, the estimated median lethal dose (LD_{50}) was 124 mg/kg in males and 98 mg/kg in females. In rats, the estimated LD_{50} was 106 mg/kg for both sexes. Tigecycline is not removed in significant quantities by hemodialysis.
This Brief Summary is based on TYGACIL direction circular W10521C013 ET01, revised 09/09.

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TYGACIL is in the 2009 IDSA/SIS guidelines for cIAI and the 2009 SIS guidelines for cSSSI.[1,2]

Expanded broad-spectrum coverage[3]* is on your side

***TYGACIL does not cover *Pseudomonas aeruginosa*.**

TYGACIL is indicated for the treatment of adults with:

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

Important Safety Information

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

Please see brief summary of Prescribing Information on adjacent page.

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

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Tygacil® tigecycline IV

Expanded broad-spectrum coverage