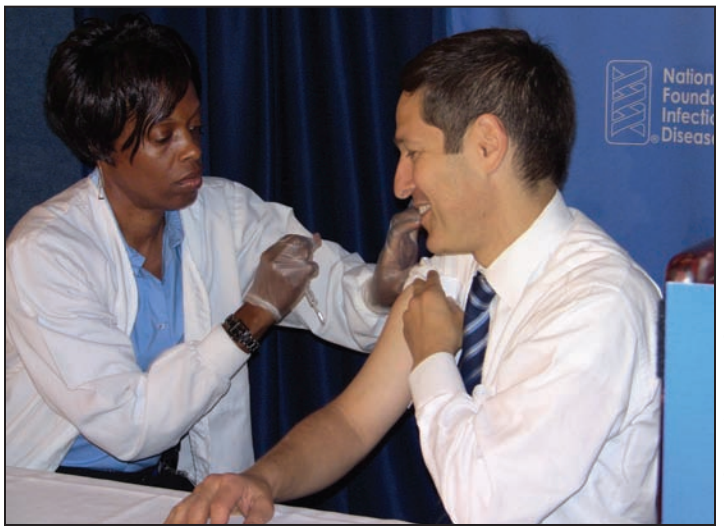
VOL. 6 • NO. 10 • OCTOBER 2011

CHEST Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS



HEIDI SPLETE/ELSEVIER GLOBAL MEDICAL NEWS

CDC Director Thomas Frieden, shown here getting his flu shot, reminded physicians that community protection begins with them.

Physician, Vaccinate Thyself Against Flu

BY HEIDI SPLETE
Elsevier Global Medical News

WASHINGTON – Flu vaccination rates in the United States are up, and more health care professionals are leading by example, Dr. Thomas Frieden, director of the Centers for Disease Control and Prevention, said at a press conference at the end of September.

The annual flu vaccine is never perfect, but "we can say with certainty that the best way to protect yourself, your family, and your community is to get a flu shot," Dr. Frieden said.

Approximately 90 million doses of vaccine are currently available, and 170 million doses are expected this year, Dr. Frieden said. Availability of the flu vaccine should not be a concern this year, and now is a great time for health care professionals and the public to get their flu vaccines, he added.

Last year, approximately 43% of Americans aged 6 months and older were vaccinated; 8 million more than the previous year, and more than ever before, Dr. Frieden said. The recommendations for flu vaccination remain the same as last year: "Everyone aged 6 months and older should get the flu vaccine, this year and every year," Dr. Frieden said. He emphasized that flu shots are necessary each year, even though the strains of flu in this year's vaccine and the viruses seen so far this year are the same as for the 2010-2011 season.

"You need this year's flu shot to protect you against this year's flu," he said. One shot should protect against the flu for the duration of the season, but protection does wane and can't be expected to carry over year to year, he explained.

This year, there are four types of flu vaccine available: the traditional intramuscular injection, a nasal spray, a high-dose injection for adults aged 65 years and older, and a new intradermal vaccine featuring a barely noticeable needle. The intradermal vaccine is only approved for use in individuals aged 18-64 years.

See **Vaccinate** • *page 4*

Endosonography For NSCLC Staging Effective, Cheaper

Patient quality of life scores higher.

BY MITCHEL L. ZOLER
Elsevier Global Medical News

AMSTERDAM – Initial endosonographic assessment of mediastinal lymph node metastases in patients with resectable non–small cell lung cancer surpassed initial surgical staging not just in clinical outcomes but also with lower cost and better quality of life in a controlled, head-to-head comparison of the two approaches.

"Given that assessment of lymph nodes by the endoscopic approach was more effective [and] better tolerated by patients, and seems cheaper than the surgical approach, we recommend that endoscopic tests be used, reserving surgical tests as a backup if endoscopy does not show evidence of cancer," Dr. Robert C. Rintoul said in presenting the results of a follow-up analysis at the World Conference on Lung Cancer.

"We think this is the way forward, and that this will change practice globally," said Dr. Rintoul, lead physician for thoracic oncology at Papworth Hospital in Cambridge, England.

He reported new data and addressed implications of the totality of evidence now available from ASTER (Assessment of Surgical Staging vs. Endoscopic Ultrasound in Lung Cancer: A Randomized Clinical Trial) that was conducted in patients with potentially resectable NSCLC.

Although the overall weight of evidence now in from ASTER uniformly favors endosonography first, perhaps the most noteworthy findings from the study were those included in a report in JAMA last November: Endosonography first cut the rate of unnecessary thoracotomies to 7% compared with an 18% rate in

See **Endosonography** • *page 8*

Cardiothoracic Surgery Losing Ground

BY BRUCE JANCIN
Elsevier Global Medical News

COLORADO SPRINGS – Is the United States truly headed for a workforce crisis in cardiothoracic surgery by 2020, as many of the field's leaders now warn?

The U.S. cardiothoracic surgery workforce is relatively old. Many practitioners are nearing retirement at a time of unprecedented demand for their services, as the baby boomers hit their Medicare years. Meanwhile, the specialty's popularity as a career choice has plummeted. It's shaping up as a "perfect storm" set to crest at the end of this decade, Dr. Sean C. Grondin, FCCP, said at the annual meeting of the Western Thoracic Surgical Association.

But this storm is not inevitable. It can be averted through a multifaceted effort that includes better mentoring programs to attract talented young people to the specialty, more emphasis on preparing instructors in surgery to teach effectively, perhaps increased reliance upon international

See **Surgery** • *page 19*

INSIDE

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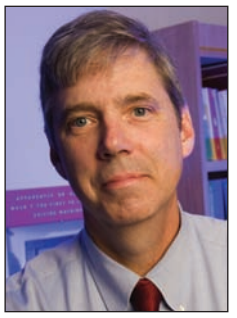
COMMENTARY

Just Stop Smoking

I give the Food and Drug Administration a "B" on their recent action to make cigarette manufacturers put graphic photos on their packaging, but I don't think it's enough. Congress could have decided on much stronger pictures. It could have made them larger, not just 20% of the pack and located on the back. In other countries that use such warnings, the pictures cover almost 80% of the packaging.



K. MICHAEL CUMMINGS, PH.D., M.P.H.

Plainly put, the United States is a Third World country when it comes to warning about cigarettes. Similar pictorial warnings have been used in Canada for almost a decade; Australia, almost all of the European Union countries, and even Uruguay have similar warnings.

Having said that, we do know that pictures speak louder than words and may help motivate smokers to quit. But here is the hard reality: Even though nearly everyone wants to quit smoking and many are trying to do so every day, the ability to sustain that motivation is not always present.

Two factors are highly predictive of a successful quit: the clinical predictor of personal biology and the financial predictor of cigarette engineering.

Biologically, some people are more prone to developing addictions than others. If you have a patient who reaches for a cigarette before their feet even hit the floor in the morning, that patient is going to need more medical assistance to be successful.

The second factor is cigarette engineering. Cigarettes are designed to get people hooked and keep them hooked. This is what makes quitting so hard despite strong personal motivation.

If we look back in history, around 1900 there were only a few hundred cases of lung cancer diagnosed in the U.S. each year. This year it will be around 160,000. What has happened since then?

People were indeed smoking then – pipes, cigars, and roll-your-own cigarettes. But it was not a daily-use situation, mostly because the pH of the smoke made it very hard to inhale. Right around 1920, commercially available cigarette brands reformulated their tobacco to make the smoke milder. This allowed people to smoke more, loading their brains up with lots more nicotine, lots faster.

Around 1950, manufacturers began adding chemicals to moderate the pH, facilitating deep inhalation into the lungs. These ingredients – diammonium phosphate, urea, and hydrochloride among them – are still on the packs' ingredient list, although they're called "flavorings."

Filters were the next step in developing an addictive product. Manufacturers presented filters as making cigarettes safer. Their real purpose was both to break down the tar into smaller particles and to force people to suck on the cigarette harder to get the smoke. Filters actually make things worse by forcing rapid inhalation and rapid absorption, delivering the nicotine to the brain within seconds.

These things were done secretly and purposefully to promote tobacco addiction and maintain profits. Tobacco companies deliberately suppressed this information until 2006, when a racketeering lawsuit forced the disclosure of dozens of documents showing the intention behind these decisions. U.S. District Court Judge Gladys Kessler determined that tobacco companies conspired to lie about the dangers of smoking and, in her 1,600-page ruling, called the conspiracy "decades long."

"In short, the defendants have marketed and sold their lethal product with zeal, with deception, with a single-minded focus on their financial success, and without regard for the human tragedy or social costs that success exacted," according to her ruling.

Despite lawsuits, public information campaigns, and the current warnings on cigarette packs, Americans continue to smoke and I continue to see the effects.

About a third of the patients I see at the Roswell Park Cancer Institute have smoking-related cancers. Imagine a vaccine that would prevent a third of cancers. The inventor would be a Nobel Laureate, globally praised.

We already have this – but it's not a vaccine. It's much simpler.

Just stop smoking. ■

DR. CUMMINGS *is the director of the New York State Smokers' Quitline and a senior research scientist at the Roswell Park Cancer Institute, Buffalo, N.Y.*

IN THIS ISSUE

CHEST PHYSICIAN Is Online
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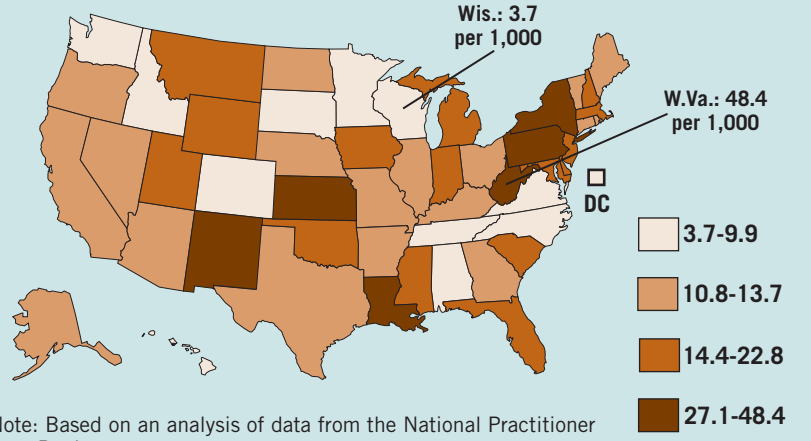
DATA WATCH

States Varied Widely in 2010 Paid Malpractice Claims
(per 1,000 physicians)



Note: Based on an analysis of data from the National Practitioner Data Bank.
Sources: Kaiser Family Foundation, Lewin Group/American Medical Association

ELSEVIER GLOBAL MEDICAL NEWS

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CHEST PHYSICIAN

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POSTMASTER: Send change of address (with old mailing label) to CHEST PHYSICIAN, 60 B Columbia Rd., 2nd flr., Morristown, NJ 07960.

CHEST PHYSICIAN (ISSN 1558-6200) is published monthly for the American College of Chest Physicians by Elsevier Inc., 60 B Columbia Rd., 2nd flr., Morristown, NJ 07960, 973-290-8200, fax 973-290-8250.

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Soviet-Era Drug Proved Effective in First Modern Study

Unlike other pharmacotherapies for smoking cessation, cytisine is inexpensive.

BY MARY ANN MOON
Elsevier Global Medical News

The compound cytisine, an extract of acacia seeds that has been used in Eastern Europe for more than 40 years as an aid to smoking cessation, was found effective in the first placebo-controlled randomized trial of the agent that meets modern regulatory standards, according to a report in the Sept. 29 issue of the New England Journal of Medicine.

Cytisine is a partial agonist that binds with high affinity to a subtype of the nicotinic acetylcholine receptor, which is also the primary target of the smoking-cessation drug varenicline. It has been available across Eastern Europe under the brand name Tabex since 1964, said Robert West, Ph.D., of the Cancer Research U.K. Health Behavior Research Centre, department of epidemiology and public health, University College London, and his associates.

Because of its "unusual history of development," no preclinical studies, dosing studies, or large comparative trials have been reported to date. "We conducted a study to assess cytisine's efficacy and safety in a context that could be replicated globally, with a relatively short treatment course (25 days) and minimal contact with health professionals," they noted.

Their aim was to determine whether the agent would be particularly beneficial for the millions of smokers who live in "countries in which the average household income is less than $200 per week and in which treatment of this kind is not paid for by insurance plans or national health care systems."

Cytisine has helped smokers quit in Eastern Europe for 47 years.

Unlike other pharmacotherapies for smoking cessation, cytisine is inexpensive; a full course of treatment costs the equivalent of $15 in Poland and $6 in Russia. This "may make it an attractive treatment option for smokers in low-income and middle-income countries," the researchers noted.

They performed a single-center, double-blind trial in which 740 subjects were randomly assigned to either active drug or placebo in equal numbers. "Behavioral support and the number of follow-up sessions were kept to a minimum to simulate, as much as possible, what might happen in a routine clinical situation" in low-income regions.

This included a baseline clinic visit where the drug was dispensed, telephone calls from staff on the target quit day (day 5) and 1 week later, a clinic visit 1 month after the target quit date, further follow-up calls, and a clinic visit for those who remained abstinent at 6 and 12 months following the conclusion of treatment.

The study participants were adults who smoked 10 or more cigarettes per day and were willing to try to stop smoking permanently. At baseline, all reported heavy smoking and showed high concentrations of carbon monoxide in exhaled breath, and all scored high on the Fagerström Test for Nicotine Dependence. Approximately half the study subjects were manual laborers, and more than 80% said they had tried to quit smoking previously.

The primary efficacy outcome was 12 months of sustained smoking abstinence after the end of treatment. This rate was 8.4% with cytisine, significantly better than the 2.4% rate with placebo.

"The net improvement in the abstinence rate with cytisine was 6 percentage points. The relative rate of abstinence in the cytisine group as compared with that in the placebo group was 3.4," Dr. West and his colleagues said (N. Engl. J. Med. 2011;365:1193-200).

This 3.4 relative difference in smoking cessation between cytisine and placebo "was higher than previous studies have shown for varenicline (2.3) and nicotine-replacement therapy (1.6). However, the absolute difference in the rate of abstinence between participants receiving cytisine and those receiving placebo in this trial (6 percentage points) was lower than that shown for varenicline and similar to that shown for nicotine-replacement therapy," they noted.

The rates of drug discontinuation or dose reduction were similar between subjects taking the active drug and those taking placebo. There were no serious adverse effects attributed to cytisine. The incidence of minor gastrointestinal adverse effects, chiefly stomach ache, dyspepsia, and nausea, was higher with cytisine than with placebo.

Using more intensive behavioral support along with cytisine may improve absolute quit rates. "Also, the treatment period was only 4 weeks, as compared with 8 weeks for nicotine-replacement therapy and 12 weeks for varenicline, and it is possible that efficacy could be improved by a longer regimen," the investigators added. ■

VITALS

Major Finding: The rate of sustained abstinence from smoking at 1 year was 8.4% with cytisine, compared with only 2.4% with placebo.

Data Source: A single-center, randomized, double-blind trial involving 370 smokers who received active drug and 370 who received placebo for 25 days and were followed for 1 year.

Disclosures: This study was supported by University College London, the U.K. National Prevention Research Initiative, Cancer Research U.K., and the U.K. National Institute for Health Research. Cytisine and matching placebo were provided at no cost by the manufacturer, Sopharma AD. Dr. West and his associates reported ties to Pfizer, McNeil, Celtic, Johnson & Johnson, and GlaxoSmithKline, and Dr. West holds a patent pending on a nicotine delivery device.

CDC: Smokers Smoking Less

BY FRANCES CORREA
Elsevier Global Medical News

Adult smokers in the United States are smoking fewer cigarettes, according to a report released by the Centers for Disease Control and Prevention.

The proportion of smokers who said they smoked 30 or more cigarettes daily decreased from 12.7% to 8.3%, according to CDC data for 2005-2010. Also, more smokers said they were smoking nine or fewer cigarettes daily, an increase from 16.4% to 21.8%. The number of adult smokers also declined from 20.9% to 19.3%, representing nearly 3 million fewer smokers.

Even as smoking prevalence has decreased overall, the data vary according to race/ethnicity, age, level of education, region, and poverty status (MMWR 2011;60:1-6). Smoking prevalence was lowest among Hispanics (12.5%) and Asians (9.2%), seniors (9.5%), those with a graduate degree (6.3%), and residents of the West (15.9%). The highest prevalence was among American Indians/Alaska Natives (31.4%), adults aged 25-44 years (22%), General Education Development (GED) certificate recipients (45.2%), and residents of the Midwest (21.8%). Categorized by poverty status, 18.3% of those at or above the poverty level smoke, compared with 28.9% of those below the poverty level.

Although smoking appears to be decreasing nationwide, the CDC said the rates have decreased more slowly in the past 5 years. A lack of investment in antismoking campaigns is one of the biggest contributing factors to the slow decline, according to Dr. Tim McAfee, director of the CDC's Office on Smoking and Health.

THE PROPORTION OF SMOKERS WHO SAID THEY SMOKED 30 OR MORE CIGARETTES DAILY DECREASED FROM 12.7% TO 8.3%.

"If states were to dedicate more like the 10%-15% that is recommended of these revenues for tobacco control, they'd be fully funding these programs and we'd be seeing a much more rapid decline in tobacco use in our society," Dr. McAfee said during a press briefing. Currently, states are contributing about 2% of their tobacco-related revenues to antismoking efforts.

Dr. McAfee added that states that invest in antismoking programs reap significant health care savings. For example, California has invested about $2.8 billion in antismoking efforts since 1988. During that same period, the state has saved nearly $86 billion in related health care costs and saw adult smoking rates decrease by about 50%, Dr. McAfee said. Smoking costs the United States $193 million annually, nearly equally divided between medical costs and loss of productivity, according to the CDC.

In addition to increased financial support for antismoking initiatives, the CDC recommends that more states place higher taxes on tobacco products and increase smoke-free policies and clinical interventions. As of 2011, 26 states and the District of Columbia have comprehensive smoke-free laws, according to the CDC. Another 18 states have smoking restrictions at work sites, in restaurants, or in bars. Also, 25 states have added clean air laws that make smoking in public more difficult, Dr. McAfee said.

The report is based on data from the CDC's 2005-2010 National Health Interview Surveys and the 2010 Behavioral Risk Factor Surveillance System survey. The analysis does not include data for underage smokers. ■

Still Room for Improvement on Flu Shot Goals

The 63.5% rate in health care personnel fell short of the Healthy People 2020 goal of 90%.

BY DIANA MAHONEY
Elsevier Global Medical News

Despite recent improvements in influenza vaccination rates among U.S. health care personnel, their rates for the 2010-2011 flu season still fell short of national health objectives, a new survey has shown.

Similarly, although the record-high influenza vaccination levels among pregnant women during the 2009-2010 influenza season were sustained during the 2010-2011 season, vaccination levels in that group also remained well below the "Healthy People 2020" target of 80% coverage for pregnant women, Dr. Carolyn Bridges said during a telebriefing on the survey results.

Influenza vaccination coverage among all health care personnel for the 2010-2011 season was 63.5%, representing an increase over the 61.9% reported for the previous year. But that rate still fell short of the Healthy People 2020 coverage goal of 90%, said Dr. Bridges of the National Center for Immunization and Respiratory Diseases.

The most recent season's results come from an Internet-based survey of 1,931 health care personnel, which the Centers for Disease Control and Prevention and the Rand Corp. conducted in April 2011.

"The vaccination rates were highest among physicians, health care personnel working in hospital settings, and those aged 60 years and older," Dr. Bridges reported.

Among the 13% of survey respondents whose workplace required influenza vaccination, the coverage rate was 98%, compared with 58% among the remaining respondents whose employers had no such requirement.

In the absence of mandatory workplace immunization, offering the vaccine onsite at work, free of charge, and on more than 1 day were associated with an increased likelihood of influenza vaccination, Dr. Bridges said.

Onsite vaccination in particular was a "key strategy," she said, noting that the coverage rate among respondents who had the onsite option was 66%, compared with 38.5% among those who did not.

With respect to influenza vaccine during pregnancy, the CDC and Rand estimated coverage for the 2010-2011 season using data from an Internet panel survey, also conducted in April 2011, among 1,457 women who were pregnant any time between October 2010 and January 2011.

In all, 49% of respondents reported receiving the vaccine, including 32% who received it during pregnancy and 17% who received it [before or after] pregnancy," said Dr. Bridges. The rate is comparable to the 50% coverage rate reported for the previous influenza season, in response to the 2009 H1N1 influenza pandemic. And it was significantly higher than the consistently low rates of approximately 15% reported in prior seasons, she said.

Pregnant women whose providers offered them the influenza vaccination were approximately five times more likely to get vaccinated than were those whose providers did not, "which is consistent with other studies," Dr. Bridges said.

Despite the fact that the influenza vaccine given during pregnancy has been shown to decrease illness in mothers and decrease the risk of influenza and hospitalization in newborns younger than 6 months old who themselves are too young to get the vaccine, "4 out of 10 women reported not receiving an offer for vaccination from their providers," she reported.

An assessment of pregnant women's attitudes and beliefs about vaccination during pregnancy determined that their top two concerns were safety risks to the baby and the possibility of getting influenza from the vaccine, Dr. Bridges stated. "Women who were offered the vaccine by their providers were more likely to have a positive attitude about the vaccine and its safety, she said.

The findings of both studies are reported in Morbidity and Mortality Weekly Report (2011;60:1073-7; 1078-82). Dr. Bridges reported no conflicts of interest with respect to the data presented. ■

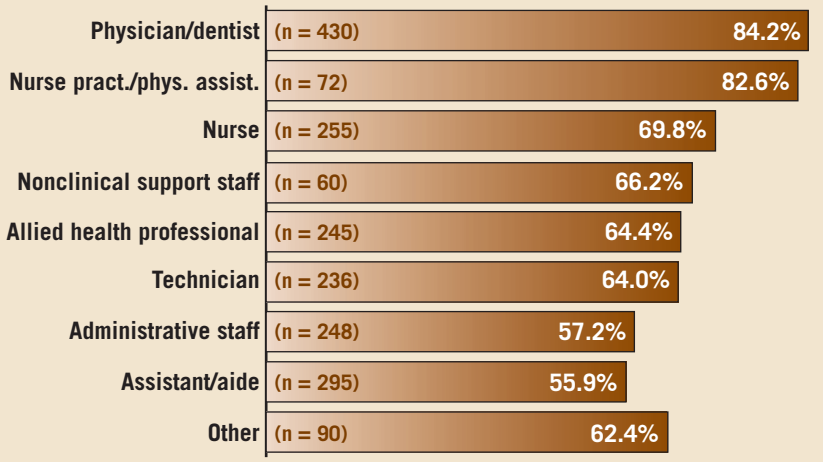
VITALS

Major Finding: Influenza vaccination coverage rates for the 2010-2011 season were 63.5% and 49%, respectively, among health care personnel and pregnant women, representing sustained or slightly higher rates than the previous season, but substantially lower than the Healthy People 2020 goals.

Data Source: Nationally representative, Internet-based panel surveys of 1,931 health care workers and 1,457 pregnant women conducted by the CDC and the Rand Corp. in April 2011.

Disclosures: Dr. Bridges reported no conflicts of interest with respect to the data presented.

Influenza Vaccination Coverage, 2010-2011 Flu Season



Note: Based on a survey conducted among health care personnel in April 2011.
Source: MMWR 2011;60:1073-7

ELSEVIER GLOBAL MEDICAL NEWS

Lead by Example With a Flu Shot

Vaccinate • *from page 1*

Approximately 51% of children in the United States received a flu vaccine last year, Dr. Frieden noted, which represents a 7% increase over the previous year. Although the news on vaccination rates is encouraging, "it is critical to continue to make progress; there are too many illnesses and deaths from influenza each year," he said.

Pediatric specialists have an important role to play in raising these rates higher, said Dr. O. Marion Burton, president of the American Academy of Pediatrics.

"Pediatricians are normally the first, and sometimes the only contact that some families have with a health care provider," Dr. Burton said. "Every child needs an influenza vaccine if they are 6 months of age or older," he said. The only contraindication is for children who have had Guillain-Barré syndrome after an immunization in the past, he said. And children with a moderate to high fever or febrile illness should not be vaccinated until the fever subsides, he said. Young children aged 6 months to 8 years who received one dose of flu vaccine last year need only one dose this year, because the vaccine formula is the same, said Dr. Burton. But children aged 6 months to 8 years who are being vaccinated for the first time this year should receive two doses at least 4 weeks apart.

Dr. William Schaffner, president of the National Foundation for Infectious Diseases (NFID), noted that vaccination rates are up among health care workers and that doctors are getting better about recommending flu vaccination to their patients.

A total of 68% of adults said that a health care professional recommended that they get a flu vaccination this year, up from 58% in 2010 and 38% in 2008, according to a nationwide telephone survey of 1,006 adults conducted by the NFID. Approximately 60% of adults who were vaccinated last year said that they did so because a health care professional specifically recommended it.

Vaccination rates in health care professionals themselves are up to approximately 63%, Dr. Schaffner said, but there is room for improvement. "There are a lot of health care professionals who still don't understand that it's a patient safety issue," he noted. "And among some health care professionals, there is that persistent myth that you can get the flu from the flu vaccine, which is incorrect," he said.

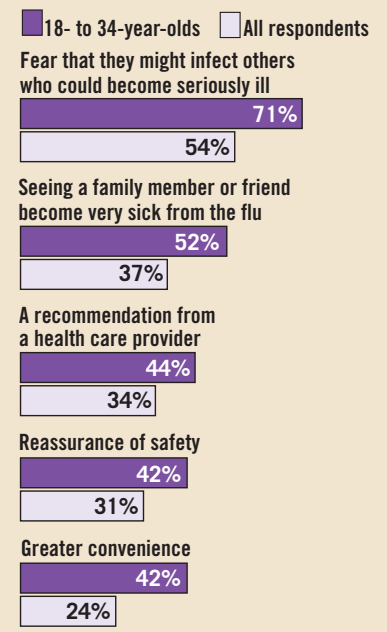
Leadership from the top is essential to improving vaccination rates in health care professionals, Dr. Schaffner said. For example, "A strong senior administrator who makes it clear that we are going to make our hospital environment absolutely as safe as possible for our patients," which means that flu vaccination is expected, "is essential for increasing flu vaccination among health care professionals," he said.

To help encourage vaccination this year, the NFID introduced a "leading by example" initiative that calls on health care professionals as well as community and business leaders to get vaccinated themselves as an example to their employees and colleagues.

Dr. Frieden set an example by getting his flu shot live during the press conference. "It didn't hurt a bit," he said.

The press conference was sponsored by the NFID. For the latest information on the 2011-2012 flu season, visit www.cdc.gov/flu or www.flu.gov. ■

Top Five Motivators for Adults to Get Flu Vaccine



Note: Based on interviews conducted Aug. 11-14 with a sample of 1,006 adults aged 18 years and older.
Source: National Foundation for Infectious Diseases

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Unusual Swine Flu Cases Have H1N1 Links

BY SHARON WORCESTER
Elsevier Global Medical News

Two swine-origin influenza A (H3N2) virus strains that triggered febrile respiratory illness in two children this summer contain genetic material from the 2009 influenza A (H1N1) virus – a genetic reassortment that hasn't been seen before, according to the Centers for Disease Control and Prevention.

The report coincides with the Food and Drug Administration's approval of a new in vitro diagnostic kit for seasonal influenza and novel influenza A viruses with pandemic potential. The kit will be distributed at no cost to qualified international public health laboratories.

Both of the H3N2 cases were reported in August. There were no epidemiologic links between the cases, and no other human infections with the virus have been detected, although investigations are ongoing, according to the CDC's report (MMWR 2011;60:1-4).

The first case involved a boy younger than 5 years, who has since recovered. The Indiana State Department of Health Laboratories reported the case Aug. 17.

The child, who had received flu vaccine in September 2010, presented in July 2011 with fever, cough, shortness of breath, diarrhea, and sore throat. A respiratory specimen taken at a local emergency department tested positive for influenza A (H3). Further testing of the specimen, including testing by the CDC, confirmed swine-origin influenza A (H3N2).

The child had no direct exposure to swine, but a caretaker of the child reported direct contact with asymptomatic swine in the weeks before onset of the boy's illness.

On Aug. 24, the Pennsylvania Department of Health reported the second case, which involved a girl younger than 5 years who also has completely recovered. That child also had received influenza vaccine in September 2010, and presented in August 2011 with acute onset of fever, nonproductive cough, and lethargy.

A nasopharyngeal swab at a local emergency department was positive for influenza A. Additional testing, including genome sequencing by the CDC, confirmed the virus as swine-origin influenza A (H3N2).

The girl had recently visited an agricultural fair, where she had direct exposure to swine and other animals.

The two viruses are similar but not identical, the CDC reported.

"Seven of the eight gene segments, including the hemagglutinin (HA) and neuraminidase (NA) genes, are similar to those of swine H3N2 influenza viruses circulating among U.S. pigs since 1998 and previously identified in the eight other sporadic cases of human infections with swine-origin influenza A (H3N2) viruses in the United States since 2009," the authors of the report noted.

There's a notable difference from those eight earlier cases, however: The two new viruses have a matrix gene from the 2009 influenza A (H1N1) virus, which has replaced the matrix gene found in the previous eight swine-origin infections in humans.

Although reassortment between swine influenza and 2009 influenza A (H1N1) has been reported in pigs, that particular genetic combination of swine influenza virus segments is unique, and has not been previously reported in swine or humans.

Researchers have since identified two additional influenza A (H3N2) isolates from swine containing the M gene from the 2009 influenza A (H1N1) virus. Those isolates are undergoing genome sequencing to characterize their genetic composition.

Although nothing is known about the new viral strains' ability to transmit efficiently in humans or swine, or between swine and humans, they have been found to be resistant to amantadine and rimantadine. They are susceptible, however, to the neuraminidase inhibitor drugs oseltamivir and zanamivir.

The CDC offered clinicians the following diagnostic and treatment recommendations:

- If influenza virus infection is suspected in an individual with recent exposure to swine, a nasopharyngeal swab should be obtained for timely diagnosis at a state public health laboratory.
- Empiric neuraminidase inhibitor antiviral treatment should be considered to quickly limit potential human transmission.

New Test Could Speed Diagnosis

The newly approved diagnostic test – the CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel – uses a three-module design that incorporates and streamlines previous versions of the CDC's two separate FDA-cleared diagnostic test kits.

The first module identifies and distinguishes influenza A and B viruses. The second module classifies influenza A viruses by subtype, such as H1N1, H3N2, or 2009 H1N1. The third module detects highly pathogenic avian influenza A (H5N1) viral infection in human respiratory tract specimens.

CDC officials are hopeful that the test, which uses specimens from a patient's upper or lower respiratory tract, will improve the ability to make quick diagnoses.

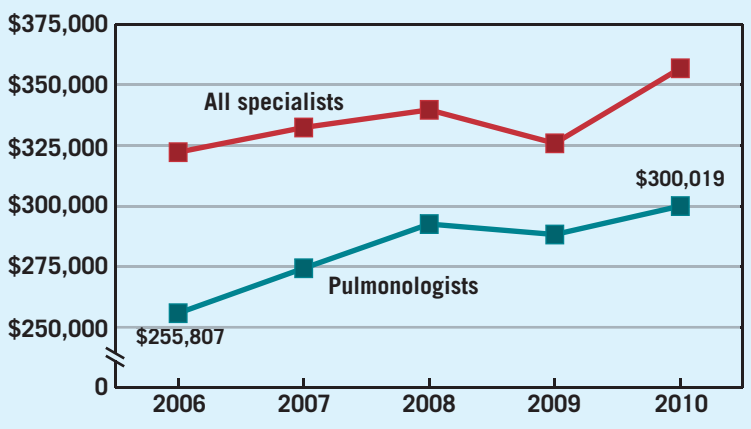
"As the spread of the H1N1 pandemic slowed last year, we conducted an end-to-end review of our nation's medical countermeasure enterprise, which showed a clear need for better diagnostic tests," Dr. Nicole Lurie, assistant secretary for preparedness and response in the Department of Health and Human Services, said in a statement.

"In helping public health officials quickly identify seasonal flu as well as the flu viruses that could become pandemic, this kit can make a real difference in protecting health and saving lives in the United States and around the world," she added.

An H3N2 virus is one of three vaccine viruses selected by the FDA for inclusion in the 2011-2012 U.S. seasonal flu vaccine, based on recommendations from the World Health Organization. The other two in the trivalent vaccine are an influenza A (H1N1) virus and an influenza B virus. ■

DATA WATCH

Pulmonologists' Median Income Rose 4.1% in 2010



Note: 2010 figure based on survey data for 253 general pulmonologists in 107 group practices.
Source: Medical Group Management Association

ELSEVIER GLOBAL MEDICAL NEWS

Most Children Who Died From Flu Weren't Vaccinated

BY HEIDI SPLETE
Elsevier Global Medical News

Nearly half the flu-related deaths in children last year occurred in those younger than 5 years, and only 23% of eligible children had been vaccinated, according to the Centers for Disease Control and Prevention.

COMMENTARY

Dr. Burt Lesnick, FCCP, comments: Every high-risk patient deserves timely administration of influenza vaccine. We should not lose opportunities to protect our patients by assuming that their primary care providers will do so.

A total of 115 flu-related deaths in children younger than age 18 years were reported to the CDC between September 2010 and August 2011. Of these, 56 (49%) had no known high-risk medical conditions as defined by the CDC's Advisory Committee on Immunization Practices. Only 17 children (23%) had been fully vaccinated, based on data from the 74 children aged 6 months and older for whom vaccination information was available (MMWR 2011;60:1233-38).

The median age of the patients who died was 6 years, and 53 deaths (46%) occurred in children under 5 years. Overall, 71 cases (62%) were associated with influenza A viruses and 44 (38%) with influenza B viruses.

"Influenza B was identified in a disproportionate number of pediatric influenza-associated deaths," although only 26% of the circulating viruses during the 2010-2011 flu season were influenza B, the researchers noted. In previous seasons, the percentage of influenza B viruses in flu-related pediatric deaths has been equal or greater than the percentage of influenza B circulating virus for that season, they said.

The data are subject to the limitations of the current surveillance system, the researchers noted. But the report emphasizes the need for continued surveillance. The CDC continues to recommend annual flu vaccinations for all children aged 6 months and older.

The MMWR also included a report on flu activity in the United States and worldwide from May 22, 2011, through Sept. 3, 2011 (MMWR 2011;60:1239-41). In the United States, 122 respiratory specimens were positive for influenza, including 87 cases of influenza A and 35 of influenza B. Flu viruses were reported in 26 states during this period, and they were different from the currently circulating H3N2 virus.

Worldwide, the 2009 H1N1 virus was the dominant circulating virus in Australia, while influenza B viruses dominated in New Zealand. The 2009 H1N1 virus also dominated cases in southern Africa, while the influenza A H3N2 was the dominant virus in Asia during this period. ■

SABR Ups Survival in Elderly With Early NSCLC

BY MITCHEL L. ZOLER
Elsevier Global Medical News

AMSTERDAM – Wide adoption of stereotactic ablative radiation as radiotherapy for elderly patients with stage 1 non–small cell lung cancer in the Netherlands produced a dramatic rise in overall survival during the last decade.

Dutch national data showed that median overall survival in patients aged 75 year or older with stage 1 NSCLC that was treated with radiation therapy jumped from 17 months in 2001-2003 to 26 months in 2007-2009 ($P = .001$), an improvement largely attributable to substantially increased use of sterotactic ablative radiation therapy (SABR), Dr. Cornelis J.A. Haasbeek said at the World Conference on Lung Cancer, which was sponsored by the International Association for the Study of Lung Cancer.

Dutch radiation oncologists began using SABR in 2003, and by 2009 more than 75% of early-stage NSCLC patients who received radiation therapy had it in the form of SABR.

"Our study provides high-level evidence to support the efficacy of modern SABR," said Dr. Haasbeek, a radiation oncologist at Vrije Universiteit Medische Centrum, Amsterdam.

SABR cut the number of treatments needed, compared with conventional radiation therapy, by 5- to 10-fold while also boosting efficacy, and is an option for patients who are too frail to undergo surgical resection of their cancer. SABR is also a reasonable option for selected operable patients, said Dr. Suresh Senan, professor and vice chairman of radiation oncology at Vrije Universiteit Amsterdam and senior investigator of the new report.

"The emerging data say that SABR is an option in patients who do not want to accept the risks of surgery, or for patients told by their surgeons that they have a significantly increased surgical risk. SABR is curative treatment for a frail group, producing excellent local control with very low toxicity," Dr. Senan said in an interview. "Elderly patients who could undergo open surgery should also be informed about SABR as an alternative curative, outpatient modality."

'The emerging data say that SABR is an option in patients who do not want to accept the risks of surgery.'

DR. SENAN

One drawback of SABR compared with surgery is less-extensive long-term experience. "We have no track record of more than 5 years in a substantial number of patients, so there may still be surprises on recurrences," he said.

"Surgery has the advantages of allowing for accurate tissue diagnosis and intraoperative staging," commented Dr. David A. Waller, a thoracic surgeon at Glenfield Hospital in Leicester, England.

'Our study provides high-level evidence to support the efficacy of modern SABR.'

DR. HAASBEEK

"The risk [from surgery] is the general anesthesia, especially in patients with existing cardiovascular morbidity. It's the patients with comorbidities who might do best with radiation therapy."

To assess the impact that SABR had on stage 1 NSCLC in elderly patients in the Netherlands during the 2000s, Dr. Senan, Dr. Haasbeek, and their associates analyzed data from the Netherlands Cancer Registry. The registry had 4,605 patients aged 75 or older with stage 1 NSCLC during 2001-2009. This included 1,678 patients who were treated with surgery (37%), 1,570 treated with radiotherapy (34%), and 1,337 treated by neither method (29%). During the 9 years reviewed, the percentage of patients undergoing radiotherapy increased from 31% of patients in 2001-2003 to 38% in 2007-2009. This paralleled a drop in untreated patients from 32% to 25%. Surgery use stayed flat over the period.

Median overall survival for all patients rose from 16 months in 2001-2003 to 24 months in 2007-2009 ($P = .001$), a change linked to survival increases in both radiation-treated patients and those who got surgery. Patients with surgical resections had a median overall survival of 36 months in 2001-2003; median survival has not yet been reached in patients who had surgery during 2007-2009.

The better median survival in the surgery patients is due in part to the superior physical status of patients eligible for surgery, Dr. Haasbeek said.

Patients who had neither surgery nor radiation therapy had a similar, poor median survival of about 7 months.

Dr. Senan has received honoraria as a speaker for and his department received research support from Varian Medical Systems. Dr. Haasbeek had no disclosures. ■

Elderly NSCLC Patients May Benefit From Doublet

BY DENISE NAPOLI
Elsevier Global Medical News

Chemotherapy with a platinum-based doublet was associated with a highly significant 36% reduction in mortality, compared with monotherapy, among elderly patients with non–small cell lung cancer in a study published by the Lancet.

The combination of carboplatin and paclitaxel was associated with more toxicity than was single-drug vinorelbine or gemcitabine regimens in the phase III trial, but the investigators contended that this was outweighed by the survival benefit.

Median overall survival for patients receiving carboplatin plus paclitaxel was 10.3 months, compared with 6.2 months in those randomized to monotherapy (hazard ratio, 0.64; *P* less than .0001).

Although several guidelines currently recommend monotherapy for elderly patients, the current finding is "of such magnitude that we believe the treatment paradigm for elderly patients with advanced NSCLC should be reconsidered," wrote Dr. Elisabeth Quoix of the Hôpitaux Universitaires de Strasbourg (France) and colleagues (Lancet 2011 Aug. 9 [doi:10.1016/S0140-6736(11)60780-0]).

The investigators from the IFCT (Intergroupe Francophone de Cancérologie Thoracique) looked at 451 patients aged 70-89 years (median age, 77 years) with unresectable stage IV NSCLC or stage III disease that was "unsuitable" for radical radiation therapy. Patients were followed for a median of 30.3 months. To be included in the study, patients had to have severe disease and a life expectancy of at least 12 weeks.

The 225 patients who were randomized to the doublet chemotherapy group received intravenous carboplatin (AUC [area under the curve] = 6), on day 1, plus 90 mg/m² of paclitaxel on days 1, 8, and 15 of 28-day cycles.

The 226-patient monotherapy cohort received 25 mg/m² vinorelbine (62 patients) on days 1 and 8 – or 1,150 mg/m² gemcitabine (164 patients) on days 1 and 8 – of 21-day cycles, with the choice of either vinorelbine or gemcitabine being made by the institution conducting the therapy.

By 1 year, the survival rate was 25.4% in the monotherapy group vs. 44.5% in the doublet therapy group (HR, 0.64; *P* less than .0001). The trend persisted at 2 years, with the probability of survival being 11.7% in monotherapy recipients and 22.4% in those receiving doublet therapy, wrote the authors.

Median progression-free survival also was significantly longer with the doublet (6 months vs. 2.8 months; *P* less than .0001).

In 2009, an independent data-monitoring committee recommended stopping recruitment based on the second interim analysis.

"Grade 3-4 neutropenia, febrile neutropenia, thrombopenia, and anemia were significantly more frequent among patients in the doublet chemotherapy group than among those in the monotherapy group, as was grade 3-4 sensory neuropathy," wrote the authors. The protocol did not allow growth factor support in the first cycle, but it was authorized as secondary prophylaxis in patients who developed grade 3 or 4 neutropenia.

In all, 10 deaths in the doublet therapy group (4.4%) and 3 in the monotherapy group (1.3%) were related to treatment: Culprit diagnoses included sepsis, respiratory distress, and diarrhea related to renal insufficiency. But the percentage of deaths in the first 3 months after the start of therapy was "markedly lower" in patients who received carboplatin plus paclitaxel.

Although quality of life scores at week 18 were similar between groups, the authors pointed out that "role functioning and fatigue were worse in the doublet chemotherapy group than in the monotherapy group" (*P* = .026 and .039, respectively). Full quality of life data will be published separately, they said.

The 2009 American Society of Clinical Oncology guidelines (J. Clin. Oncol. 2009;27:6251-66) recommend that age "not be used as a criterion in the decision-making process about whether to treat a patient" and call for further research devoted to elderly patients, according to Dr. Quoix and colleagues. "Conversely," they noted, "the European Organisation for Research and Treatment of Cancer Elderly Task Force and Lung Cancer Group and International Society of Geriatric Oncology highlighted in 2010 that monotherapy should be given to elderly patients with advanced NSCLC."

"We believe that monthly carboplatin and weekly paclitaxel is a feasible option for first-line therapy of advanced NSCLC in patients older than 70 years with performance status scores of 0-2," the authors wrote.

The study was funded by the IFCT and the French National Cancer Institute, with support by grants from Bristol-Myers Squibb, Roche, and Pierre Fabre. Several authors, including Dr. Quoix, disclosed financial relationships with the makers of chemotherapy drugs, including carboplatin (Bristol-Myers Squibb, Roche, and Lilly). ■

Resection an Option for High-Risk NSCLC Patients

Study suggests surgery is feasible for many patients considered high risk for pulmonary resection.

BY BRUCE JANCIN
Elsevier Global Medical News

COLORADO SPRINGS – Patients with stage 1a non–small cell lung cancer deemed medically inoperable or high risk can undergo surgical resection safely and with excellent outcomes, judging by results of a single-center retrospective study.

In this study, their perioperative morbidity and mortality and 5-year recurrence-free survival rates were similar to those of low-risk patients undergoing tumor resection, Dr. Andrea S. Wolf said at the annual meeting of the Western Thoracic Surgical Association.

"These outcomes in high-risk patients provide the standard to which nonoperative therapies should be compared," said Dr. Wolf of Brigham and Women's Hospital, Boston.

Of the 170,000 new cases of non–small cell lung cancer diagnosed annually in the United States, 80% are deemed inoperable because of extensive malignancy or severe comorbidities, including chronic obstructive pulmonary disease, which affects about half of patients with NSCLC. Stereotactic body radiation therapy (SBRT), which uses advanced imaging techniques to deliver a targeted radiation dose to a tumor, is making substantial inroads in these inoperable patients. But Dr. Wolf's study suggests that surgery is still feasible for many patients considered high risk for pulmonary resection.

She reviewed the records of 66 patients with stage 1a disease considered high risk and 158 low-risk controls, all of whom underwent surgical resection at Brigham and Women's Hospital during 1997-2006. None had pure bronchoalveolar carcinoma. Patients were deemed high risk if they were aged 80 years or older, or if their forced expiratory volume in 1 second (FEV_1) was 50% or less of the predicted amount. Forty percent of the high-risk patients met the age criterion, 60% met the diminished pulmonary function standard, and 5% fulfilled both. Pathologic findings were similar in the high- and low-risk groups, with a median tumor size of 1.5 cm.

With a median 6 years of follow-up, the local recurrence rate was 18% in the high-risk population and 16% in the low-risk cohort. The distant recurrence rate was 15% in both groups.

The 5-year overall survival rate was 54% in the high-risk group and significantly better at 68% in the low-risk group ($P = .04$). However, there was no significant difference in 5-year recurrence-free survival: 73% and 77% in the high- and low-risk groups, respectively.

Perioperative mortality occurred in 2% of low-risk patients and none of the high-risk patients. The perioperative major morbidity rate was 14% in the high-risk group and 8% in the low-risk group. Similarly, there were no significant between-group differences in the rates of any individual major complications, which included MI, pulmonary embolus, and reoperation for bleeding.

"Your rationale is right on target," discussant Dr. Joseph B. Shrager told Dr. Wolf. "It's highly important in this era of SBRT to document the excellent results we can get with surgery in very-high-risk patients. And zero deaths, which is what you showed here and was equivalent to the experience with low-risk patients, is certainly admirable."

That being said, he added that he was disappointed with the Boston surgeons' paltry use of anatomic resection in the high-risk group. Only 18% underwent lobectomy and another 6% received segmentectomy, while 76% had a wedge resection.

"There were less than one-tenth as many segmentectomies as wedges in the high-risk patients. So, really, what you've shown is that a lesser operation – or you might even say our least-good operation – can safely be done in high-risk patients. The question now is, is that lesser operation better than SBRT? Because if it's not, then SBRT will probably win that argument. I have to say, I think we have a better chance of winning out over SBRT with surgery if we're comparing it to segmentectomy than if we're comparing it to wedge," said Dr. Shrager, professor and chief of the division of thoracic surgery at Stanford (Calif.) University.

Dr. Wolf replied that, like Dr. Shrager, she and her coinvestigators were "surprised" at the high rate of wedge resection because thoracic surgeons at Brigham and Women's Hospital tend to promote anatomic resection whenever possible. She suspects some of the wedges were performed in an effort to spare parenchyma when a tumor bordered segmental boundaries.

Dr. Shrager also took the Boston surgeons to task for the fact that only 38% of high-risk patients in the series underwent lymph node sampling.

"Short of a proven survival advantage for surgery over SBRT, which we don't have yet, all we can say is at least we're providing better lymph node staging. So why not more lymph node sampling?" Dr. Shrager asked.

Dr. Wolf said this, too, came as a surprise to her and her colleagues. The most likely explanation is that in many instances patients and surgeons sought smaller, quicker operations in an effort to spare the patient. But given the compelling evidence showing that lymph node sampling is critical for accurate staging and for determining the need for adjunctive therapy, that's not an adequate excuse.

"Going forward, we're very interested in making sure nodes are sampled, even with wedge resections," she said.

Dr. Wolf declared having no financial conflicts. ■

COMMENTARY

Dr. Richard Fischel, FCCP, comments: The results of this study may indicate that higher-risk patients can safely undergo a surgical procedure, but it does not provide any real evidence that surgery in these patients is any better than noninvasive radiation procedures. I must agree with the discussant that the very high rate of wedge resections and the lack of lymph node dissections does little to forward the argument that surgery may be advantageous. While it is encouraging to know that a quality center can perfom lung resections in a higher-risk population (we routinely operate on patients over 80 years of age with excellent results), this study does not answer the question of whether that operation was advantageous for the patient. The theoretical major advantage of surgery is pathologically clear margins and proper staging. Certainly additional studies will be required to evaluate the surgery versus SBRT or cyberknife treatment question.

Noninvasive Staging

Endosonography • *from page 1*

patients assessed by mediastinoscopy first ($P = .02$). In addition, 45% of patients evaluated by endosonography first had positive lymph nodes and so avoided mediastinoscopy (JAMA 2010;304:2245-52).

"A few years ago, people said all these patients need mediastinoscopy. What we've learned [from ASTER] is that about half never need mediastinoscopy. That is practice changing," commented Dr. Richard Gralla, chief of hematology oncology at North Shore–Long Island Jewish Health System in New Hyde Park, N.Y. "As a rule, patients find EBUS [endobronchial ultrasound–guided transbronchial needle aspiration] and EUS [transesophageal ultrasound–guided fine-needle aspiration] much simpler procedures," compared with mediastinoscopy, he noted at the meeting, which was sponsored by the International Association for the Study of Lung Cancer.

The ASTER results published last year proved so compelling that many surgeons and thoracic oncologists have already switched to endosonography first, noted Dr. Jouke T. Annema, a thoracic surgeon at Leiden (the Netherlands) University and lead ASTER investigator.

"EBUS is the new standard," he said in an interview, noting that earlier this year the Dutch agency responsible for setting medical policy adopted endosonography as the preferred initial method for lymph node assessment in patients with resectable NSCLC. The National Institute for Health and Clinical Excellence (NICE), which sets U.K. health policies, did not name endosonography as the preferred initial staging method for lung cancer in its revised guidelines last April because the cost-effectiveness findings reported at the meeting had not yet been published, Dr. Rintoul said.

'We think this is the way forward, and that this will change practice globally.'

DR. RINTOUL

ASTER randomized 118 patients to initial mediastinoscopy staging and 123 to initial endosonographic staging at four medical centers in the United Kingdom, the Netherlands, and Belgium. Results showed that initial endosonography followed by surgical staging in patients initially found to be node negative had 94% sensitivity for finding positive lymph nodes, which was significantly better than the 79% sensitivity rate using mediastinoscopy first ($P = .02$).

The additional analyses reported by Dr. Rintoul used patient quality of life assessment by the EQ-5D (EuroQol five-domain) instrument at baseline, immediately after staging, and again at 2 and 6 months after staging. Researchers ran EQ-5D assessments on 144 of the study's 241 patients at baseline, and on 124 patients after 6 months. The results showed similar average EQ-5D scores at baseline and after 2 and 6 months; however, immediately after staging, the endosonography-first patients had a statistically significant edge in average quality of life (0.117 EQ-5D units), compared with those staged by mediastinoscopy first ($P = .003$).

Average medical costs rung up by patients over the 6 months of treatment after baseline were about £746 (about $1,200) less per patient using endosonography first, a difference that was not statistically significant but suggested that initial endosonographic staging produced better cost-effectiveness, Dr. Rintoul said. He also reported that initial endosonography led to an average gain per patient of 0.015 quality-adjusted life-years, an advantage over initial surgical staging that just missed statistical significance ($P = .052$).

ASTER received no commercial support, and Dr. Rintoul said that he had no disclosures. He said that Papworth Hospital has received unrestricted educational grants and equipment loans from Olympus. Dr. Gralla and Dr. Annema had no disclosures. ■

Donor Lung Allocation Faulted

BY BRUCE JANCIN
Elsevier Global Medical News

COLORADO SPRINGS – A disproportionate share of donor lungs goes to local, low-priority recipients, according to an analysis of data from the United Network for Organ Sharing.

The current lung allocation system results in a high proportion of donor organs being distributed to low-priority candidates who often receive little survival benefit from their transplant. Meanwhile, higher-priority candidates who might derive more benefit from transplantation continue to die at high rates on the waiting list, Dr. Alexander Iribarne said at the annual meeting of the Western Thoracic Surgical Association.

He presented an argument for the sharing of donor lungs over a broader geographical range in the United States. The analysis involved all 7,171 U.S. lung transplants done between May 2005 and the end of 2010.

May 2005 was chosen as the starting date because that's when the Lung Allocation Score (LAS) was introduced as a measure for allocating organs on the basis of medical urgency rather than waiting time. An LAS score lower than 50 defines a transplant candidate as low priority, a score of 50-75 is considered intermediate, and an LAS greater than 75 is high priority.

Among the 5,544 transplants done in low-priority recipients, 54% of the donor organs were allocated locally, 17% regionally, and 29% nationally. In contrast, 40% of the 1,016 transplants in recipients with an LAS of 50-75 at the time of surgery were allocated locally, as were 33% of the donor organs used in patients with an LAS over 75.

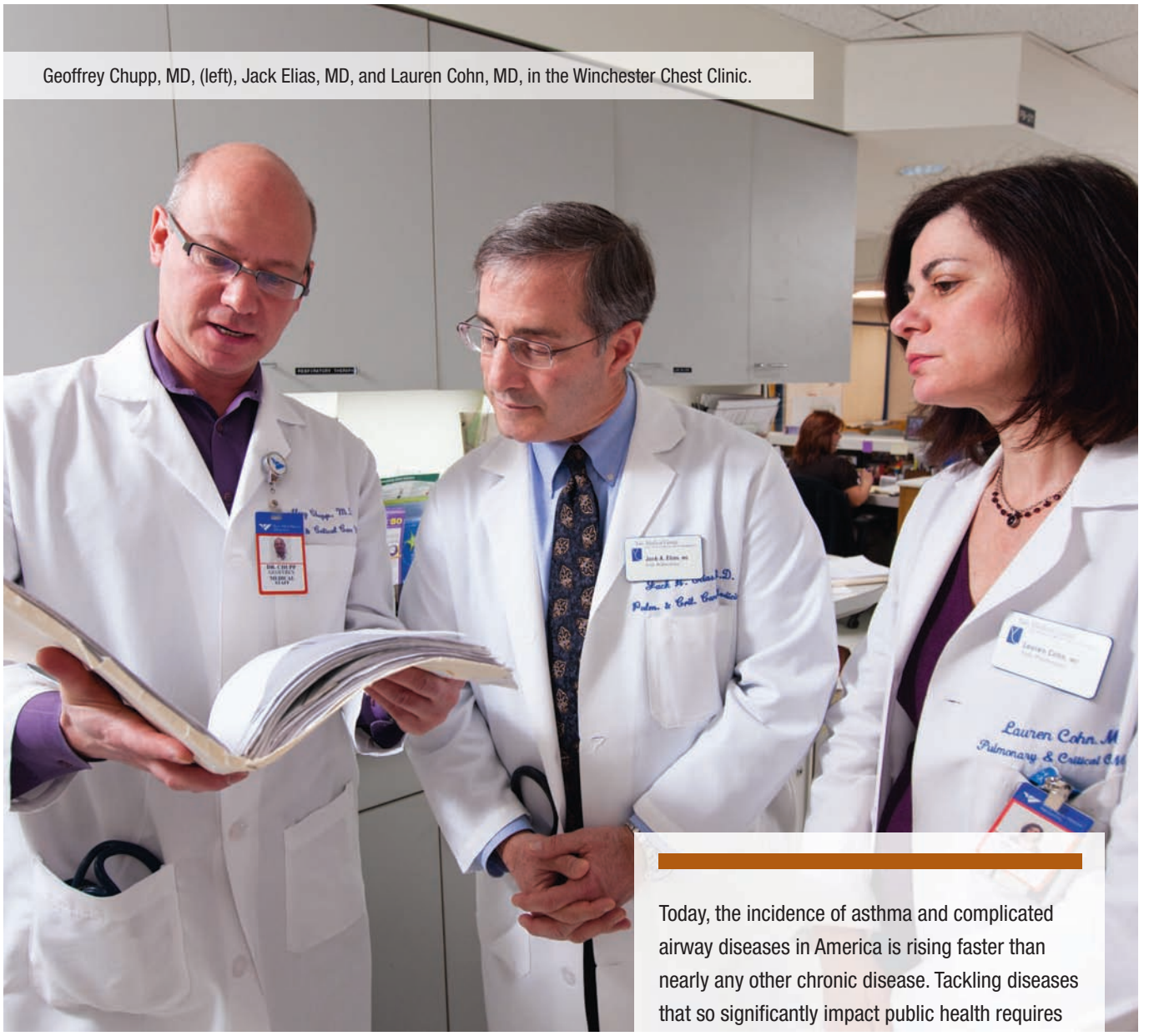
What's happening is that when an organ becomes available in one of the less-populated local donor service areas, there's a lower likelihood that a suitable higher-priority candidate will be in place than in a more populous donor service area, said Dr. Iribarne of Columbia University, New York.

As a result, the organ often goes to a local patient with an LAS under 50.

The UNOS data showed that in donor service areas with a population of fewer than 6.1 million, nearly 75% of locally allocated lungs went to patients with an LAS under 50. In local donor service areas with a population in excess of 10.3 million people, a greater percentage are allocated to higher-priority recipients, Dr. Iribarne said.

The next step should be to determine whether organ sharing across broader geographical areas results in higher rates of lung allocation to higher-priority candidates, he added.

Dr. Iribarne declared having no financial conflicts. ■



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

COPD Prevalence Doubled in Rheumatoid Arthritis

BY SARA FREEMAN
Elsevier Global Medical News

LONDON – Patients with rheumatoid arthritis have a high risk of concomitant chronic obstructive pulmonary disease, according to data from two studies.

In one of the studies – which involved more than 15,000 patients with rheumatoid arthritis (RA) and 15,000 healthy individuals as case-matched controls – the risk of the long-term lung condition was 8.9% vs. 4.4%, respectively (*P* less than .001).

Other data, from the Norfolk Arthritis Register (NOAR), showed that the prevalence of chronic obstructive pulmonary disease (COPD) in patients with inflammatory polyarthritis (IP) or RA was 7.3% (n = 425) at 15 years' follow-up. Prevalence of the respiratory disease was again doubled when compared to the general population.

"Lung involvement is a common extra-articular manifestation in rheumatoid arthritis," said Dr. Suzanne Verstappen, who presented the findings from the NOAR at the annual European Congress of Rheumatology.

VITALS

Major Finding: COPD was a comorbid condition in 8.9% of patients with rheumatoid arthritis compared with 4.4% of controls from the general population in one study (*P* less than .001), with 7.3% of the Norfolk Arthritis Register study population also found to have the respiratory disease.

Data Source: A case-control study of more than 30,000 individuals with or without rheumatoid arthritis and data from a 15-year follow up of 435 patients with inflammatory polyarthritis or RA in the Norfolk Arthritis Register.

Disclosures: The Norfolk Arthritis Register is funded by Arthritis Research UK. Dr. Verstappen and Dr. Amital and colleagues had no conflicts of interest to declare.

"As could be expected, age and gender were associated with obstructive and restrictive lung disease," said Dr. Verstappen, a research fellow at the Arthritis Research UK Epidemiology Unit at the University of Manchester, England, where the NOAR is coordinated.

Validated spirometry parameters and the Medical Research Council respiratory symptoms questionnaire were used to identify patients with IP or RA who also had COPD. The latter was distinguished from restrictive lung disease. The prevalence of restrictive lung disease was 9.7%.

COPD was observed in 7.3% of the population at 15 years, with higher prevalence rates found in men versus women over the age of 45 years (12.7% vs. 6%, respectively) in a crude comparison. Published rates for the U.K. general population without IP or RA are 6.8% and 3.9% (Popul. Health Metr. 2007;5:8).

The disease manifests later in life and treatment is symptomatic rather than curative, as the obstruction in the airways is permanent and only partially reversible with bronchodilator and other therapies. Unlike RA, however, which has multiple etiologic factors and autoimmunity at its root, COPD is most frequently caused by smoking. In the NOAR analysis, 53% of the 425 patients were ex-smokers and 13% were current smokers; 34% had never smoked.

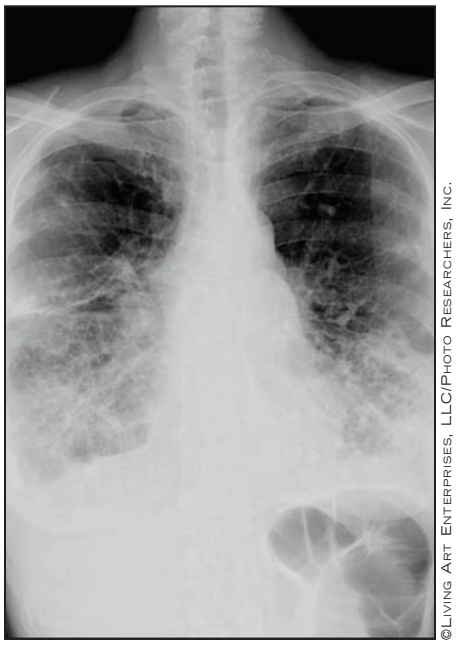
Data from the first study, presented during a poster session by Dr. Howard Amital of Sheba Medical Centre in Tel Hashomer, Israel, showed, however, that even with smoking out of the equation, the risk of COPD in patients with RA was higher than in the general population.

Indeed, multivariate analysis showed that RA was associated with COPD after the researchers controlled for confounding factors such as age, gender, smoking, obesity and socioeconomic status.

"The strength of the association increased," Dr. Amital and colleagues reported, with an adjusted odds ratio (OR) of 2.015 (95% confidence interval 1.83-2.22; *P* less than .001) and an unadjusted OR of 1.89 (95% CI 1.74-2.05, *P* less than .0001).

The case-control study involved 15,766 patients with RA and 15,240 age- and sex-matched healthy individuals without RA. The study also found higher rates of other chronic disease in patients versus controls, including diabetes (23.9% vs. 19.8%, *P* less than .0001), ischemic heart disease (19.5% vs. 15.4%, *P* less than .0001), and heart failure (6.3% vs. 4.3%, *P* less than .0001).

"This study corroborates the hypothesis that COPD and RA are closely interrelated," Dr. Amital and his team concluded. ■



©Living Art Enterprises, LLC/Photo Researchers, Inc.

This frontal radiograph shows evidence of COPD and chronic interstitial lung disease in a patient with rheumatoid arthritis. More RA patients have COPD, compared with controls.

COMMENTARY

Dr. Darcy Marciniuk, FCCP, comments: The results from these studies highlight the reality that COPD is significantly underdiagnosed – in this case, in patients with rheumatoid arthritis. The reason(s) why COPD (diagnosed objectively with spirometry) was twice as common in patients with rheumatoid arthritis compared to the general control population is not known, but is very interesting and deserving of further study.

A related finding was that restrictive lung disease was also commonly diagnosed.

The strong take-home message is to objectively assess pulmonary function in rheumatoid arthritis patients who have respiratory symptoms.

FDA Approves Arcapta Neohaler for COPD Patients

BY EMILY HAYES
Elsevier Global Medical News

The Food and Drug Administration has approved the Arcapta Neohaler for chronic obstructive pulmonary disease, albeit at a single and much lower dose than the two doses originally sought.

Novartis AG's Arcapta (indacaterol inhalation powder) was approved at a 75-mcg once-daily dose for long-term maintenance treatment of airflow obstruction in COPD, including chronic bronchitis and/or emphysema, the FDA announced.

The long-acting beta$_2$–adrenergic agonist helps muscles around the airways of the lungs stay relaxed in order to prevent symptoms of COPD.

As expected, a boxed warning in labeling and a medication guide note that the LABA class increases the risk of asthma-related death and that the bronchodilator is not indicated for asthma.

The approval was hard won, following much debate about the appropriate minimum dose for good efficacy and following a "complete response" letter in October 2009. Novartis had most recently been pushing for approval of two doses: 75 mcg and 150 mcg. But safety concerns for the LABA class in patients with asthma have been high on the agency's radar. The FDA's Pulmonary-Allergy Drugs Advisory Committee voted in March for the approval of the 75-mcg dose only.

In its original New Drug Application in 2008, Novartis sought approval for 150-mcg and 300-mcg doses, which were subsequently approved in Europe. But the FDA's "complete response" letter contended that these doses were high and questioned the supporting data.

In response, Novartis lowered its requested doses to 75 mcg and 150 mcg and submitted additional data from six confirmatory trials in more than 5,000 patients, who had a smoking history of at least a pack a day for 10 years and moderate to severe decreases in lung function, the FDA noted in its announcement of the approval. In the six trials, efficacy was measured based on changes in forced expiratory volume testing. With this measure, all doses tested (75 mcg, 150 mcg, 300 mcg, and 600 mcg) showed improvements in lung function at 12 weeks, compared with placebo, the label notes.

The label also notes that pooled data from the six studies show an improvement in health-related quality of life, based on patients' results on the St. George's Respiratory Questionnaire.

Although the quality of life data showed an advantage for the higher dose, in the end, the FDA advisory committee was not persuaded that the 150-mcg dose had an efficacy advantage that would balance the higher risks.

Novartis intends to launch the drug in the first quarter of 2012. ■

Ms. Hayes *is with "The Pink Sheet." This newspaper and "The Pink Sheet" are published by Elsevier.*

Smoking Speeds Loss of Lung Function in COPD

BY JEFFREY S. EISENBERG
Elsevier Global Medical News

The rate of change in forced expiratory volume in 1 second among patients with COPD is highly variable, with the greatest rates of decline occurring among current smokers, patients with bronchodilator reversibility, and those with emphysema, according to an analysis of data from the ECLIPSE observational study.

Research in the 1970s established that patients with COPD experience an accelerated decline in FEV_1, yet few longitudinal studies have provided detailed data about this decline.

Dr. Jørgen Vestbo of the University of Copenhagen and his colleagues analyzed data collected for the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study, which included 2,163 patients aged 40-75 years who had a smoking history of 10 or more pack-years and 80% of the predicted value and ratio of FEV_1 to forced vital capacity (FVC) of 0.7 or less (N. Engl. J. Med. 2011 Sept. 26 [doi:10.1056/NEJMoa1105482]).

Specifically, the researchers analyzed changes in FEV_1 after bronchodilator use at baseline, 3 months, 6 months, and then every 6 months for 3 years. They defined subgroups according to the presence of emphysema and chronic bronchitis, bronchodilator reversibility, and cardiovascular disease. They also obtained serum and plasma samples for the following biomarkers: C-reactive protein, interleukin-8, interleukin-6, fibrinogen, tumor necrosis factor–alpha, surfactant protein D, and Clara cell secretory protein 16 (CC-16).

The rate of FEV_1 was highly variable during the 3-year period, the results showed. Overall, there was a mean decline of 33 mL/year. More specifically, 38% of patients had a decline of more than 40 mL/year, 31% had a decline of 21-40 mL/year, 23% had changes ranging from a decline of 20 mL/year to an increase of 20 mL/year, and 8% had an increase of more than 20 mL/year.

The researchers also found an inverse relationship between the declines in FEV_1 and stage of disease, as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD). Mean rates of decline were 35 mL/year in patients with moderate disease (GOLD stage 2), 33 mL/year in patients with severe disease (GOLD stage 3), and 25 mL/year in patients with very severe disease (GOLD stage 4).

Smoking status was most strongly associated with the rate of decline, with current smokers experiencing a decline of 21 mL/year more than former smokers. However, cumulative exposure did not affect future decline.

Among the subgroups studied, FEV_1 declined by 17 mL more per year in patients with bronchodilator reversibility at baseline, compared with those without reversibility. Also, FEV_1 declined by an additional 13 mL/year in patients with clinically significant emphysema versus those with little or no emphysema. The presence of cardiovascular disease had no effect on FEV_1.

Although several biomarkers were associated with FEV_1 at baseline, only CC-16 levels were significantly associated with the rate of change in FEV_1, with an additional decline of 4 mL/year for each decrease of 1 standard deviation in the level of CC-16, but the association was weak, the researchers said.

The study findings call into question whether COPD is invariably progressive. "COPD may 'burn out' or at least stabilize for periods of 3 years or more, which would be good news for patients and could influence a variety of management decisions that depend on prognosis."

A limitation of the study was that it included only patients with moderate, severe, or very severe COPD, and therefore could not identify factors associated with rates of decline in early-stage COPD. Also, the study was purely observational and did not include treatment. "Our results may not extend beyond this patient population for a variety of reasons, including the clinically determined care they received," the researchers said.

The study was supported by grants from GlaxoSmithKline to Dr. Vestbo and several coauthors. Some of the coauthors are employees of and own stock in GlaxoSmithKline. All coauthors reported ties to numerous pharmaceutical companies. ■

PAUL A. MARKOWSKI, CAE

FROM THE EVP/CEO

ACCP by the Numbers

I'm a numbers guy. If a picture paints a thousand words, then numbers, for me, equate to tens of thousands of words. Accordingly, we use numbers a lot at the College to track our progress. The ACCP strategic plan features rigorous metrics, and we created a dashboard of key performance indicators for leaders and staff to readily spot changes and trends and focus on what matters most.

While numbers may not tell an entire story, they can be revealing. With that in mind, the following numbers illuminate the ACCP in a way that would be difficult to do with words alone.

- Total number of members in 2001: 15,256
- Current total number of members: 18,172
- Total number of international members in 2001: 2,528
- Current total number of international members: 3,556
- Current number of members in India: 370
- Current number of members in Uganda: 1
- Total number of attendees at the CHEST 2000 annual meeting: 3,840
- Total number of attendees at the CHEST 2010 annual meeting: 4,721
- Total number of international attendees at the CHEST 2000 annual meeting: 768
- Total number of international attendees at the CHEST 2010 annual meeting: 1,383
- Number of staff working at ACCP headquarters in 2001: 62
- Current number of staff working at ACCP headquarters: 84
- CME credits offered in 2001: 268
- CME credits offered in 2010: 627
- Participants claiming CME in 2000: 2,131; in 2010: 3,794
- Percentage of lecture-based programming in 2001: 100
- Percentage of lecture-based programming in 2011: 49
- Percentage of simulation-based programming in 2001: 0
- Percentage of simulation-based programming in 2011: 21
- Number of manuscripts submitted to the *CHEST* journal in 2000: 1,980
- Number of manuscripts submitted to the *CHEST* journal in 2010: 3,300
- Ranking of the *CHEST* journal among respiratory journals in 2000: 8th (Journal Citation Reports®)
- Ranking of the *CHEST* journal among respiratory journals in 2010: 3rd (Journal Citation Reports®)
- Number of ACCP apps in 2008: 0
- Current number of ACCP apps: 3
- Fans on Facebook in 2008: 0
- Current number of fans on Facebook: 1,515

(Information current as of September 1, 2011.)

Many ACCP leaders and staff are responsible for the tremendous growth cited here. I would like to thank Dr. David D. Gutterman, FCCP, in particular, for the instrumental role that he has played in the progress of the College, as President this past year and in his 19 years serving the ACCP in a variety of leadership capacities. David's thoughtful leadership and unwavering dedication to the College are directly responsible for our renewed commitment to diversity, expanded global reach, nimble advocacy, enhanced governance, and streamlined pathways to meaningful member involvement, to name a few of his enduring contributions. I look forward to continuing to work with—and the ACCP will undoubtedly continue to benefit from—David in his new role as Immediate Past President.

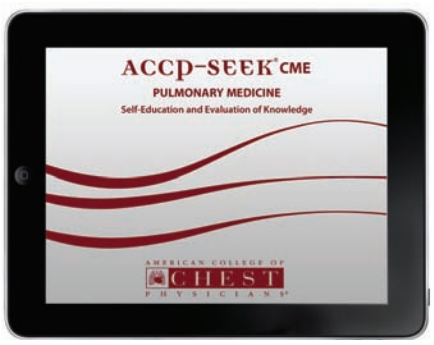
And, one final statistic—the number of global leaders providing education in cardiopulmonary, critical care, and sleep medicine to optimize health and advance patient care: 1. ■

Product of the Month

ACCP-SEEK® App: Now Offered as CME Edition

Various volumes of ACCP-SEEK® have been available as an app for iPhone®, iPad®, and iPod touch® for 2 years, but, until now, the downside to the app as compared with the book has been the app's lack of CME credit. The ACCP is pleased to release a new app that addresses this need: ACCP-SEEK® CME features complete questions from the just-released *ACCP-SEEK® Volume XXI: Pulmonary Medicine* book and allows users to earn 50 CME credits on completion of all in-app questions and an online posttest. Like the print volume, the ACCP-SEEK® CME app costs $199.99—less than $4/credit. Users can download the app and sample 10 case-based questions for free via the App Store. The CME app retains all the same great features as the original: search and browse questions by keyword, star questions for follow-up, record text and audio notes, link to references in an online browser, and more.

The original, non-CME-eligible app has also been updated to include the same case-based questions from the *ACCP-SEEK® Volume XXI: Pulmonary Medicine* print book. Because CME is not available for any activities performed in this app, sets of 10 questions are available for the reduced price of $4.99.



COURTESY ACCP

Download ACCP-SEEK® CME and start on your way to 50 CME credits at http://bit.ly/SEEKCME.

Download the original ACCP-SEEK®, and study at the reduced price, without CME credit at http://bit.ly/ACCPApp. ■

This Month in *CHEST:* Editor's Picks

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

ORIGINAL RESEARCH

▶ **Diagnosis of Pneumothorax by Radiography and Ultrasonography: A Meta-analysis.** *By Dr. W. Ding et al.*

▶ **Surgical Management and Outcomes of Elderly Patients With Early Stage Non-small Cell Lung Cancer: A Nested Case-Control Study.** *By Dr. C. Rivera et al.*

▶ **Mitral Annular Calcification Predicts Cardiovascular Morbidity and Mortality in Middle-aged Patients With Atrial Fibrillation: The Belgrade Atrial Fibrillation Study.** *By Dr. T. S. Potpara et al.*

POINT/COUNTERPOINT EDITORIALS

▶ **Point: Should Tele-ICU Services Be Eligible for Professional Fee Billing?**
Yes. *Tele-ICUs and the Triple Aim. By Dr. M. M. McCambridge et al.*
No. *By Dr. S. Hoffmann.*

Vaccination Pocket Guides

Pocket guides for health professionals on the latest recommendations for influenza and pneumococcal vaccines are now available from the Immunization Action Coalition. The "2011-12 Influenza Vaccine Pocket Information Guide" reflects the most current recommendations and issues in use for the vaccine. These include (1) rationale for why it is important to get this year's vaccine, even though the vaccine viruses did not change from the previous year; (2) which children need two doses of vaccine; (3) vaccination of persons with egg allergy; (4) the addition of an intradermal form of inactivated vaccine; and (5) the different age indications for the various vaccine products.

The "Pneumococcal Polysaccharide Vaccination Pocket Guide" is also available. The card is the same as the card distributed last year, as there are no changes in the recommendations.

Both pocket guides are available at no cost. To order either or both pocket guides in quantity, go to http://www.immunize.org/pocketguides/.

For up-to-date information on influenza, visit the Web site of the National Influenza Vaccine Summit at www.preventinfluenza.org. ■

ACCP to Welcome New President at CHEST 2011

Suhail Raoof, MBBS, FCCP, will be inaugurated as the 74th President of the American College of Chest Physicians during the Convocation Ceremony at CHEST 2011.

He is Professor of Clinical Medicine at Weill Medical College of Columbia University and Chief of Pulmonary/Critical Care and Sleep Medicine, Medical Director of Respiratory Therapy, and Vice-Chairman of the Department of Medicine at New York Methodist Hospital in Brooklyn, New York.

DR. SUHAIL RAOOF, FCCP

Dr. Raoof obtained his medical degree from Maulana Azad Medical College, Delhi University, India. He completed his medical residency at Long Island Jewish Medical Center in New York, followed by a fellowship in pulmonary and critical care medicine at the State University of New York at Stony Brook and its affiliated hospitals.

Dr. Raoof has served the ACCP in many capacities, including Chair of the US and Canadian Council of Governors, Chair of the Membership Committee, member-at-large of the Board of Regents, Chair of the CHEST 2008 Annual Scientific Program Committee, Chair of the Council of Committees, Chair of the Global Education Track for CHEST 2010, ACCP representative to the American College of Radiology, and ACCP representative to the European Respiratory Society's multisociety effort to develop noninvasive ventilation guidelines.

Dr. Raoof's academic interests include mechanical ventilation and chest radiology for pulmonologists.

Dr. Raoof is the recipient of many honors, including Master of the American College of Physicians (MACP). Dr. Raoof's vision for the ACCP during his term will be to continue to promote the ACCP as a leader in clinical chest medicine and make available to the membership cutting-edge initiatives to deliver evidence-based medical education. He plans to facilitate the development of problem-based learning modules for clinicians in chest radiology. He also endeavors to keep the membership informed of new and emerging health-care needs, so they can incorporate best medical practices in their day-to-day patient care and partner with the College for their recertification, licensure, and educational needs. Dr. Raoof will promote leadership development and mentorship within the College. He will continue to strengthen collaboration with strategic international partners. Finally, by promoting the OneBreath™ Campaign, he hopes to encourage virtual participation of the lay public through social media and increase awareness of pulmonary diseases and develop new partnerships with health-care societies and others.

We asked Dr. Raoof about his vision for this upcoming presidential year.

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

The last 2 years have defined a new paradigm in how the ACCP Presidents operate. As part of a concerted 3-year plan that commenced when I was elected President-Designate, I will continue to promote diversity in every aspect of the College, facilitate in redefining the work of the NetWorks and Governors, and foster transparency and openness. These are important projects that were initiated by our prior two Presidents--Drs. Guntupalli and Gutterman. Strengthening ties with targeted international partners (societies, individuals, and industry) and strategic international regions will continue to evolve. As the needs of our membership grow, the College will continue to retool and refine educational projects, including simulation, train-the-trainers, and certificate of completion programs, and provide multiple mediums of educational content to its members. It will also be my endeavor to strengthen our collaboration with sister organizations, such as the ATS, CTS, SCCM, ACP, AACN, and ERS. Perhaps the most important project that we have launched is "mentorship and leadership development." As a College, we should strive to instill in our members the ability to act as agents of change and to inspire and mentor others to rise to their fullest potential. And finally, the infrastructure of the College requires a strong financial base. The EVP/CEO, Board of Regents, and the Presidents have the fiduciary oversight responsibility for the College, which I will take very seriously.

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

The greatest strengths of the College are its excellence in imparting clinically focused, high quality chest education globally; its networking opportunities; the continuous stream of new and innovative ideas that emanate in a timely fashion from the collaborative team efforts between dedicated physician membership and talented staff; and its warm and welcoming collegial atmosphere.

Simulation education, train-the-trainer and certificate of completion courses, clinical practice guidelines, performance improvement modules, and Web-based educational content should be made available to the entire membership locally and globally. A new association management system (AMS) that supports and integrates with a new content management system (CMS) and learning management system (LMS) will leverage technology platforms to complement the vast educational content provided at our live courses for physicians and nonphysician health-care providers. Team-based training will enhance our members' knowledge and equip them with tools to better provide patient-focused and evidence-based care to their patients. Incorporating social media will allow dissemination of information to diversified generations and groups throughout the cross-section of ACCP membership, and new ACCP e-communities will enhance communication among leadership, members, and sister organizations. It will be my utmost endeavor during my presidency to uphold the principles of governance dedicated to transparency, economic effectiveness, and commitment to the mission, vision, and core values of the ACCP.

What are some challenges facing the ACCP, and how will you address these challenges?

While there are several issues that confront the College, including shifting revenue streams, changing generational needs of the membership, retention of members and expansion of the membership base, health-care reform, workforce shortage, and coordination of an integrated team approach, I would like to focus on the changing health-care landscape and poor public awareness of pulmonary diseases.

Health-care reform has introduced a sense of insecurity and "fear of the unknown" in our members, especially those in private practice. The College is poignantly aware that its members expect their professional society to have its ear to the ground so that it can monitor the changing health-care landscape and provide important and accurate information and balanced, well-thought-out remedial measures, so members can react appropriately, adapt proactively, and develop solutions expediently. We are in the process of setting up an intricate infrastructure under the Governors that will utilize grassroots education within the entire spectrum of College leadership, as well as designated staff for advocacy and regulatory issues. The members of the Chest Medicine Affairs Committee will energize and inform

Continued on following page

NETWORKS

Saturation and POCs, New Role for Affiliates, Interventional Pulmonology

Airways Disorders

Saturation in Portable Oxygen Concentrators

AG is a 75-year-old woman diagnosed with COPD 2 years earlier. Her room air oxygen saturation is 90% to 91% at rest. Treadmill oxygen titration revealed desaturation below 88%. She was prescribed 3 L via nasal cannula with saturation increasing to 98% at rest and 92% with exercise. Her physician decides to prescribe 3L via nasal cannula. Oxygen equipment was delivered to her home. She wanted portable equipment for daily activity and traveling and chose a light piece (6 lbs) portable oxygen concentrator (POC) that delivers 3L via pulsed flow.

Today, she is complaining that the POC does not feel the same as her home equipment or the oxygen she received when the treadmill titration was performed.

This, unfortunately, is too common a situation that arises in practice. Many POCs deliver only pulsed oxygen with only a few delivering continuous flow, and these tend to be larger and heavier and not preferred by patients.

Although the technology is improving, pulsed-dose oxygen does not deliver the same oxygen concentration as continuous flow. Thus, 3L delivered from wall oxygen is not the same as 3L from POC with pulsed flow.

Patients should have oxygen saturation tested during activity while receiving pulsed-dose oxygen. Moreover, pulsed flow should not be used during sleep. POCs flow is triggered by nasal inhalation, and mouth breathers will not get oxygen flow.

Most POCs also are not capable of delivering an adequate saturation level nocturnally for the patient. Continuous flow should generally be prescribed for sleep.

What matters are not the liters but the saturation, taking into account patients' preferences.

Dr. Rubin Cohen, FCCP
NetWork Vice-Chair

Affiliate

New Role for the Affiliate NetWork

At its June meeting, the ACCP Board of Regents approved a recommendation to evolve the Affiliate NetWork into a standing committee of the ACCP. The new Training and Transitions (T&T) Committee will expand on the previous role of the Affiliate NetWork to oversee a greater number of educational activities within the College. These will include:

- Continue to provide a structure for Affiliate members to actively participate in the College.
- Oversee all fellows' courses presented by the ACCP.
- Create and implement a successful Leadership Development program.
- Develop a sustainable mentoring and coaching program for Affiliate members.
- Monitor educational and resource needs of Affiliate members.
- Oversee the CHEST Challenge program.
- Create resources to assist members in career decisions and development of Affiliate members.

This new committee will work closely with NetWorks, the Education Committee, and other key groups within the ACCP to meet its educational mission. To ensure proper representation of our Affiliate members, the committee's policy stipulates that at least three members of the Training and Transitions Committee be ACCP Affiliate members, and at least three members must be either Program Directors or Associate Program Directors at their home institution.

We are very excited to see this expanded role and value the ACCP's recognition and support of training and developing our professional society's future leaders.

If you have interest in getting involved in the ACCP's Training and Transitions Committee, please contact Rachel Gutterman at rgutterman@chestnet.org.

Dr. Jack Buckley, FCCP
NetWork Chair

Interventional Chest/Diagnostic Procedures

The Evolution of Interventional Pulmonology

What began as rigid bronchoscopy over 50 years ago has been transformed into interventional pulmonology (IP) this century. This domain largely falls under the purview of specialty-trained pulmonary medicine physicians and general thoracic surgeons. The field has evolved to include interventions directed toward the diagnosis, treatment, and staging of a variety of disease processes, including thoracic cancers, tracheobronchial obstruction, small airways disease, and pleural processes.

The field requires a multidisciplinary approach, as the problems are often quite complex and span several medical subspecialities. To this end, close collaboration between pulmonology and general thoracic surgeons trained in advanced IP techniques is essential.

Specifically, emerging technologies, such as endobronchial ultrasound and navigational bronchoscopy, are gaining widespread acceptance as important diagnostics that are routinely employed by IP practitioners.

More importantly, care centers interested in developing an IP program should focus not simply on IP technicians but also highly trained nursing, respiratory therapy, and anesthesia teams.

Dr. Sudish Murthy, FCCP
NetWork Chair

Pulmonary Vascular Disease

Exercise and Pulmonary Hypertension

The role of exercise in the diagnosis and treatment of pulmonary arterial hypertension (PAH) has evolved. Years ago, patients were encouraged to minimize their activity to avoid overwhelming the stressed right ventricle. With the advent of agents to treat PAH, this approach has changed.

The benefits of pulmonary rehabilitation are well established for left ventricular systolic dysfunction. Recent studies suggest similar findings for right ventricular dysfunction. For example, Mereles et al (*Circulation*. 2006;114[14]:1482) demonstrated that patients with PAH benefited from guided exercise training as measured by the 6-min walk test, Vo2 max, workload at anaerobic threshold, and quality of life. This program utilized stationary cycling, walking, and low impact weight training and was closely supervised.

Pulmonary hemodynamic response to exercise may identify patients with PAH who have normal or modest elevation of pulmonary artery pressure (PAP) at rest.

Tolle and colleagues (*Circulation*. 2008;118[21]:2183) identified a subset of patients with heightened pulmonary artery response to exercise. Some 406 patients referred for evaluation of dyspnea had pulmonary artery catheterization and cardiopulmonary exercise testing. They found a subset of patients with normal resting PAP who developed increased PAP and pulmonary vascular resistance with exercise.

Saggar and colleagues (*Arthritis Rheum*. 2010;62[12]:3741) examined patients with scleroderma and normal resting pulmonary hemodynamics. They found distinctive patterns that included normal response, pulmonary venous hypertension, and exercise-associated PAH.

These findings suggest that exercise may be beneficial to patients with known PAH and may help to diagnose PAH earlier in a patient's course.

Dr. Victor Test, FCCP
NetWork Steering Committee Member

Continued from previous page

others on various committees in understanding how best to navigate these regulatory challenges. The leadership and staff will work together to provide structure and empower the efforts of these groups.

The second and more generic age-old problem pertains to poor public awareness and lack of branding of pulmonary diseases. The College needs to help bridge this chiasm in public awareness. Through the philanthropic arm of the College, The CHEST Foundation and its OneBreath™ Campaign, the College hopes to reach out to the public, educate them on the importance of lung conditions, and garner support for chest diseases and fund research. "OneBreath™: Make The Most Of It" is an initiative that aims to improve lung and heart health by providing valuable prevention resources, raising public awareness, and encouraging community-based activities that people who care about their heart and lungs can follow.

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

Get involved. Join ACCP NetWorks. Become part of the e-communities. Sign up for the mentorship program. Link up with talented professionals who have spent their lives mentoring junior colleagues. Be a co-chair or moderator at annual CHEST meetings. Submit interesting cases to the "Case Puzzler" sessions at CHEST. Submit manuscripts to the *CHEST* journal. Use the ACCP social media outlets. Participate actively in the OneBreath™ Campaign. Reach out to the leadership and the Presidents of the College with new ideas. Reach out to the College! We are ready and waiting for you!

Congratulations, Dr. Raoof! ■

Pulmonary Perspectives

Aerosolized Prostacyclin vs Inhaled Nitric Oxide

Pulmonary hypertension (PH) is a serious disease that arises from several different etiologies: pulmonary vascular, lung, or cardiac diseases. In addition to chronic disorders, acute events, such as acute respiratory distress syndrome (ARDS), pulmonary embolism, acute left ventricular dysfunction, or cardiothoracic surgery, can also cause PH (Zamanian et al. *Crit Care Med*. 2007; 35[9]:2037). PH occurs primarily through the down-regulation of endogenous vasodilators (nitric oxide and prostacyclin) and the up-regulation of the endogenous vasoconstrictor endothelin-1 (Weitzenblum and Chaouat. Pulmonary Circulation: Diseases and Their Treatment. 2nd Edition. New York, NY: Oxford University Press; 2004:376; Ishikawa et al. *J Thorac Cardiovasc Surg*. 1995; 110[1]:271). The consequence of this imbalance is increased pulmonary vascular resistance (PVR), eventually leading to right ventricular hypertrophy and ischemia. Systemic vasodilators, while effective in decreasing pulmonary artery pressure (PAP) and PVR, may induce systemic hypotension and worsen right ventricular function. Local administration of vasodilators through inhalation can reduce PAP and PVR with minimal effects on systemic arterial pressure. In addition, inhaled vasodilators may improve arterial oxygenation by redistributing pulmonary blood flow to ventilated areas of the lung and reduce intrapulmonary shunt (Lowson. *Anesthesiology*. 2002;[6]:1504; Kemming et al. *Eur Surg Res*. 2002; 34[1-2]:196).

Inhaled nitric oxide (iNO) was the first inhaled vasodilator investigated and has gained widespread off-label clinical use for PH due to various causes (Lowson. *Anesthesiology*. 2002;96[6]:1504; Kemming G. *Eur Surg Res*. 2002;34[1-2]:196). Nitric oxide (NO) is a gaseous molecule that is synthesized endogenously from the amino acid L-arginine via nitric oxide synthase. The primary effects of NO include vasodilation of pulmonary vessels secondary to activation of soluble guanylate cyclase, inhibition of platelet aggregation and leukocyte adhesion, and modulation of bronchomotor tone (Riddell and Owens. *Vitam Horm*. 1999;57:25; Hickey and Kubes. *Exp Physiol*. 1997;82[2]:339; Giaid and Saleh. *N Engl J Med*. 1995;[4]:214). NO has a half-life of about 3 to 50 s, and standard doses used in clinical practice range from 5 to 40 ppm (Ignarro. *Circ Res*. 1989;65[1]:1; Dellinger et al. *Crit Care Med*. 1998;26[1]:15). NO is inactivated via hemoglobin. Methemoglobinemia can be a byproduct, but this is uncommon with doses < 40 ppm (Jindal and Dellinger. *J Lab Clin Med*. 2000;136[1]:21). Although several trials have evaluated iNO for acute lung injury (ALI), none have demonstrated significant mortality benefit (Taylor et al. *JAMA*. 2004;291[13]:1603; Jindal and Dellinger. *J Lab Clin Med*. 2000;136:21). In addition, its use is limited by cost and need for special delivery equipment. As such, there is a growing interest for potential alternatives, such as aerosolized prostacyclin (prostaglandin I_2, epoprostenol).

Epoprostenol (PGI_2), a prostacyclin derivative, is formed by arachidonic acid metabolism. It stimulates adenylate cyclase receptors to activate cyclic adenosine monophosphate and protein kinase A, resulting in smooth muscle relaxation and pulmonary vasodilation. PGI_2 has a short half-life of 3 to 6 min, with the most common adverse effect from systemic administration being hypotension (see Flolan® package insert). Epoprostenol can also be aerosolized via jet or ultrasonic nebulization, which offers the advantage of lower systemic side effects while effectively achieving pulmonary vasodilation (Siobal. *Respir Care*. 2004;49[6]:640). Additionally, epoprostenol has no known toxic metabolites, and its inhalation could be considerably safer and cheaper than iNO (De Wet et al. *J Thorac Cardiovasc Surg*. 2004;127:1058).

iNO vs PGI_2: Pulmonary Hypertension

Inhaled PGI_2 was compared with iNO for the management of primary (n=7) and secondary (n=5) PH. All patients received PGI_2 at increasing doses of 15 to 50 ng/kg/min for a period of 20 min with a 10-min washout between doses, while eight patients received iNO at doses of 10 to 100 ppm, as well as IV prostacyclin at doses of 1 to 5 ng/kg/. Hemodynamic measurements were taken before, during, and after each treatment. Nebulized PGI_2 produced greater decrease in PAP (54 ± 5 to 44 ± 5 mm Hg, P =.0005) compared with iNO (54 ± 5 to 48 ± 5 mm Hg, P =.02), as well as PVR (38% vs 12 %, respectively, P =.0001). No dose-dependent effect of inhaled PGI_2 was identified, which suggests that lower doses could be used to attain significant response. There was no change in systemic arterial pressure with either agent (Mikhail. *Eur Heart J*. 1997;18[9]:1499). Short-term effects of aerosolized PGI_2 (52-112 mcg/kg/min), iNO (10-28 ppm), and iloprost were compared in six patients with PH. PGI_2 was nebulized for 15 min and resulted in greater reduction in pulmonary hemodynamics: PAP (18%), PVR (41%) (P <.05). There was a significant improvement in CO and SvO_2 and a nonsignificant change in systemic arterial pressure (Olschewski. *Ann Intern Med*. 1996;124[9]:820). Another study evaluated short-term response after 10 min of aerosolized PGI_2 (20-30 mcg via nebulization) compared with iNO (40 ppm) in 10 patients with PH awaiting heart transplantation. Both PGI_2 and iNO had a similar effect on mean PAP (7% reduction) and PVR (49% vs 43% reduction, respectively), while PGI_2 had a significantly greater effect on CO (11% increase vs 0%) (Haraldsson. *Chest*. 1998;114[3]:780).

iNO vs PGI_2: Following Cardiothoracic or Transplant Surgery

Inhaled PGI_2 (3 mcg/min) and iNO (20 ppm) were examined in 58 intubated patients with mitral valve stenosis and elevated PVR after mitral valve surgery. Drugs were given for 30 min followed by a 15-min washout. PGI_2 and iNO significantly reduced PVR (50% vs 45%, respectively), mean PAP (20% vs 19%, respectively), and transpulmonary gradient (TPG) (64% vs 62%, respectively) (Fattouch et al. *J Card Surg*. 2005;20[2]:171). These same authors also reported significant reductions in mean PAP and PVR with inhaled PGI_2 and iNO compared with systemic therapy, as well as significant improvements in cardiac indices, weaning from cardiopulmonary bypass, and shorter intubation times and ICU stay (Fattouch et al. *J Cardiovasc Med*. 2006;7[2]:119).

Inhaled PGI_2 has also been evaluated following lung and heart transplantation in 25 patients who were randomized to inhaled PGI_2 (20,000 ng/mL) or iNO (20 ppm) as initial therapy, followed by a crossover to the other agent after 6 h. Both PGI_2 and iNO similarly improved hemodynamics (cardiac index [CI], central venous pressure [CVP], SvO_2) and PAP initially and at the 6-h crossover trial (change in mean PAP: 13 ± 1 mm Hg, 95% CI 9-16 and 12 ± 1 mm Hg, 95% CI 9-15, respectively. P =.32). Neither agent affected the oxygenation index or systemic blood pressure (Khan. *J Thorac Cardiovasc Surg*. 2009;138[6]:1417).

iNO vs PGI_2: ARDS

Five patients with hypoxemia secondary to ARDS were examined after receiving 30 min of either iNO (10 ppm) or aerosolized PGI_2 (50 ng/kg/min) in a crossover study. The increase in PaO_2 post PGI_2 therapy (29%) compared with iNO (12%) was not statistically significant (P =.06). Hemodynamic parameters (mean arterial pressure, CI, CVP, pulmonary capillary wedge pressure) and shunt fraction did not change significantly (van Heerden et al. *Anaesth Intens Care*. 1996;24[5]:564). Inhalation of NO and PGI_2 was compared in a dose-response study in eight patients with ARDS (1, 4, 8 ppm and 1, 10, 25 ng/kg/min for 15 min each, respectively). PGI_2 resulted in significant, dose-dependent reduction in mean PAP, while iNO did so only at 4 and 8 ppm. PGI_2 reduced PVR by 20% at 10 ng/kg/min only, while iNO had no significant effect on PVR. Increases in PaO_2 were significant with PGI_2 doses of 10 (+18%) and 25 (+ 24%) ng/kg/min and all doses of iNO, with 8 ppm resulting in the greatest increase (+ 45%). Only iNO produced a significant decrease in intrapulmonary shunt (Zwissler. *Am J Respir Crit Care Med*. 1996;154[6]:1671-1677; Lowson. *Anesthesiology*. 2002;96[6]:1504). Both agents were investigated in a dose titration study for 48 h to find maximum improvement of arterial oxygenation and the lowest effective dose in 16 patients with ARDS. Mean doses of iNO and PGI_2 that resulted in similar and significant increase in PaO_2/FIO_2 and significant decrease in intrapulmonary shunt were 17.8 ± 2.7 ppm

Continued on following page

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

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

Comment From the Guest Editor

Pulmonary hypertension is a life-threatening condition that, left untreated, portends a poor prognosis. Although the pathophysiology of PH is not fully understood, it is known that the condition involves an imbalance between endogenous vasodilators and vasoconstrictors. Several novel therapeutic strategies to combat PH are currently under investigation. Inhaled PGI2 demonstrates potential as an effective, yet safe, option for treating patients with PH. We look forward to further investigation and development of aerosolized prostacyclins for the treatment of PH.

DR. MARSHALEEN HENRIQUES-FORSYTHE, *Director, Pulmonary Hypertension Clinic, Morehouse School of Medicine, Atlanta, GA*

Continued from previous page

and 7.5 ± 2.5 ng/kg/min, respectively. Inhaled PGI_2 produced a significantly greater decrease in mean PAP and PVR than iNO, with little impact on systemic arterial pressure (Walmrath et al. *Am J Respir Crit Care Med*. 1996;153[3]: 991-6). The use of iNO and inhaled prostacyclin in ARDS and ALI has been recently reviewed (Puri and Dellinger. *Crit Care Clin*. 2011; 27[3]:561-87; Siobal and Hess. *Respir Care*. 2010;55[2]:144).

Conclusion

Based on the available evidence, it appears that inhaled PGI_2 is as effective as iNO for short-term management of PH and impaired oxygenation with potentially fewer side effects, lower costs, and greater ease of administration. However, further randomized, controlled studies are needed to prove the efficacy of inhaled PGI_2 and determine its place in therapy for patients with PH. ■

Marina Rabinovich, PharmD;
Derek Burden, PharmD;
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Sample Checklist for Physician Retirement

BY DONNA K. KNAPP, MA, FACMPE
Vice-Chair, Practice Management Committee

Preparations for retirement should start on your first job. All of the details to create a successful retirement can take as little as a minute or as long as decades to accomplish properly. The following is a general list of issues to consider when planning your retirement. The list is not all inclusive and is not to be considered legal advice. All individual life, health, and family situations should be considered from a personal perspective. It is important to speak to an expert in financial planning and an estate advisor as early in your career as possible and on a regular basis. Addressing the following issues will get you started on the road to a comfortable living in your retirement years:

Personal Living Issues

- A home free of debt, in good repair, with low maintenance upkeep, easily maneuvered and with enough room for an in-house caretaker
- Transportation free of debt, in good repair, with low maintenance upkeep, easily maneuvered, and with adequate storage capacity for personal living equipment

Insurances

- Long-term care bought at the peak time for the best lifetime rate—consult your insurance broker
- Enough life insurance to cover all debts and provide for surviving spouse
- Health insurance with coverage options when traveling
- Vision, dental
- Long-term and/or short term disability if still working or plan to work part-time
- Home, auto, general liability, and umbrella coverage

Physician Practice

- Profit sharing, pension, and/or 401K pretax benefits funded to the maximum allowed by law every working year
- Review of retirement plan documents for the terms and options of paying out the pretax benefits after termination
- Shareholder/employment agreement that specifies preretirement slowdown options and termination of employment notification requirements
- Buyout agreement that specifies the formula and timeframe for shareholder funds to be distributed upon departure
- Continuous trend analysis of buyout distribution formula when provided with practice reports
- Analysis of any restrictive covenants of the shareholder/employment and buyout agreements to ensure other local part-time, charity, temporary, etc, employment options after retirement from the practice

Documents

The following documents should be completed at the beginning of your career, kept current, and updated immediately when there is a life change:

- Durable and Health Care Power of Attorney with advance directive completed
- Will to specify the distribution of all of your personal assets and let your wishes for memorial services be known
- Living Trust Agreement to assign assets to your trust and instruct your executor on their distribution
- Prenuptial/Mutual Agreement if sharing assets or living with a person who is not a legal spouse to protect and/or distribute assets according to your wishes upon your relationship departure or your death

Retirement planning should be started early, be vigilant throughout your career, and always be working toward the retirement goals that you have set for you and your family. ■

Critical Care Commentary

ICU Transitions: Patients, Families, and Staff

Patients in the ICU face a number of health transitions from the time they enter the hospital until they are discharged. A transition is defined as a "process or period in which something undergoes a change and passes from one state, stage, form, or activity to another" (*Encarta World Dictionary*, 1999). While transitions may involve new roles, such as becoming a mother or starting a new job, health transitions are complex and multidimensional. This is especially so in the transition from being a regular patient to becoming a critically ill one or being a regular family member to being a family member of an ICU patient. Such transitions require the rapid incorporation of new knowledge, possible behavioral adjustments, and a change in a person's definition of "self." Assisting patients and their families in coping with health transitions has long been part of the nursing role (*Image*. 1994;26:119). Recent studies have focused on the 'patient journey' through the continuum of care. (Ben-Tovim et al. *Med J Aust*. 2008;188[suppl 6]:S14).

There is limited research on patients' transitions into the ICU, perhaps because such admissions are often unplanned. Once patients are in the ICU, however, they, and their family members, have a profound need to "feel safe." They need to overcome the ICU-engendered anxiety, depression, fear, and high stress levels (acute stress disorder, posttraumatic stress disorder, and posttraumatic stress reaction) (McAdam and Puntillo. *Am J Crit Care*. 2009;18[3]:200). Research has also shown that the ICU environment is so unexpected and difficult that families are affected both socially and economically (Agard and Harder. *Intensive Crit Care Nurs*. 2007;23[3]:170). The key to accomplishing this safe feeling is the close observation, vigilant care, and personal interaction provided by the ICU nurse (Hupcey. *J Nurs Scholarship*. 2000;32[4]:361).

Similarly, transfer out of the ICU has been identified as a particularly stressful time for both patients and families. Common themes have emerged from interviews with patients and families about the ICU transfer to the hospital ward. These include feelings of sudden abandonment, vulnerability and helplessness, unimportance; and ambivalence about the entirety of the ICU experience (Chaboyer et al. *Aust Crit Care*. 2005; 18[4]:138). "Transfer anxiety" and "relocation stress" are two terms that have been coined to capture this experience. Caregivers of chronically ill patients report a high level of lifestyle restrictions and stress, especially if their loved ones never returned home or regained their preadmission health status after ICU discharge (Choi et al. *Am J Crit Care*. 2011;20[1]:12). Therefore, supporting the caregivers is an important task for health professionals during ICU and hospital discharge transitions.

In addition to psychological issues, recent evidence suggests that patients are at particular risk for adverse events (ie, patient injury as a result of healthcare change and not the underlying condition) following transfer out of ICU. In a cohort study of 300 consecutive patients, a total of 147 adverse events were identified in patients in the 72 h after transfer from the ICU (Chaboyer et al. *Am J Crit Care*. 2008;17[3]:255). Others have shown that 52% of adverse events experienced by patients in the 72 h following ICU transfer were potentially preventable (McLaughlin et al. *Anaesth Intensive Care*. 2007;35[4]:486). Additionally, post-ICU mortality may be related to the time of day of ICU discharge, with increased mortality associated with after-hours ICU discharge (Lin et al. *Aust Crit Care*. 2009;22[1]:29), although this relationship is not universally accepted.

From the health service perspective, this body of work complements two recent patient safety initiatives, clinical handover and recognizing and responding to the deteriorating patient. Clinical handover (or hand-offs) is much more than the transfer of information; it also involves transferring responsibility and accountability for patient care (*The OSSIE Guide to Clinical Handover Improvement*. Sydney, Australia: Australian Commission on Safety and Quality in Health Care; 2010). Recent campaigns, such as the World Health Organization's "High 5s," have raised awareness of the risks associated with poor clinical handover. Miscommunication during handover poses a major risk for adverse events (Bomba and Prakash. *Aust Health Rev*. 2005;29[1]:68; Joint Commission's *Perspectives on Patient Safety*. 2005;5[2]:1-2) and can lead to discontinuity of care (van Walraven et al. *J Gen Internal Med*. 2004;19[6]:624). One European study showed that 28% of medical ICU transfer reports contained at least one critical or serious error (Perren et al. *Intensive Care Med*. 2008;34[11]:2054). The second patient safety initiative, recognizing and responding to the deteriorating patient, has its foundation in Australian research that identified clinical signs and symptoms that were exhibited by patients in the hours prior to cardiac arrest (Franklin and Matthew. *Crit Care Med*. 1994; 22[2]:244; Harrison. *Resuscitation*. 2006;71[3]:327). Yet, these warning signs go unnoticed. Clinical staff may not have the knowledge and skills to safely identify and care for acutely ill ward patients at risk of serious deterioration (Cioffi. *Heart Lung*. 2000;29[4]:262).

Health service providers and researchers have responded to both the physical and psychosocial risks associated with ICU transfer in a number of ways. Critical Care Outreach Teams (CCOT) in the United Kingdom and ICU Liaison Nurses (LN) in Australia are but two examples. These nurse-led services focus on following-up patients discharged from the ICU, in addition to assisting the ward staff in caring for patients with complex needs or who are at risk of deterioration. Such nursing teams provide psychosocial and practical support to the patient and family in addition to physical support to the patient.

The next major transition ICU patients face is their transition out of the hospital. A recent review of long-term complications of critical care identified that physical, psychiatric, and cognitive complications can last for 5 to 15 years (Desai et al. *Crit Care Med*. 2011;39[2]:371). These limitations are pulmonary, neuromuscular, and physical in nature, whereas others reflect depression, anxiety, post-traumatic stress disorder, and delirium. Deficits in most quality of life domains have also been consistently identified and have resulted in hospital and outpatient initiatives. For example, avoidance of medications, such as corticosteroids and neuromuscular blocking agents, and glycemic control have been advocated to address critical care illness neuromyopathy. Early mobility and rehabilitation in the ICU and its continuation throughout the recovery period have also been suggested to promote better physical functioning and prevent muscle atrophy, as has limiting deep sedation. Lighter sedation or daily sedation interruption have also been advocated to limit psychiatric complications. But, as Desai and colleagues note (*Crit Care Med*. 2011;39[2]:371), the evidence for most of these initiatives is only beginning to emerge.

Health-care professionals may benefit from using the "theory of illness representations" (Leventhal et al. *Handbook of Health Psychology*. Mahwah, NJ: Lawrence Erlbaum Associates Publishers; 2001) when helping patients and families adjust to these transitions. Illness representations are reflections of how people develop and use their own interpretation of their illness conditions. Both cognitive and emotional representations are used to determine individuals' illness-related behaviors in response to health threats and their adjustments and coping with these changes. In numerous patient populations, illness representations have been associated with quality of life and functional outcomes. Application of this theory may assist health professionals in gaining an understanding of their patients' illness perceptions and develop more accurate perceptions, if required. Techniques, such as cognitive behavioral therapy, can be used to reshape erroneous perceptions.

As more patients are being admitted to the ICU and also surviving their ICU experiences, it seems important to continue investigating not only their recovery but also their transitions and how we can help patients and their families in this endeavor. And, if we really want to understand the patient and family journeys, then we will have to undertake this research with their collaboration, extending their right to participate in their care to their right to be active members of the research team. Ultimately, this paradigm shift reflects the simple idea leaders in patient safety have been advocating—"If it's about me, not without me." ■

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DR. NEIL HALPERN, FCCP
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Lessons for October

PCCSU
PULMONARY, CRITICAL CARE, SLEEP UPDATE

▶ **Acid-Base Disorders.** *By Dr. Deepa Bangalore; and Dr. Janice L. Zimmerman, FCCP*

▶ **Necrotizing Fasciitis and Deep Soft Tissue Infections in the ICU.** *By Dr. Oluwaseun Falade-Nwulia; and Dr. Naomi P. O'Grady*

Pao_2 Criterion for Lung Transplant Questioned

BY MITCHEL L. ZOLER
Elsevier Global Medical News

PHILADELPHIA – It may be time to reassess the commonly held belief that donor lungs that are headed for transplantation should have an arterial blood gas partial pressure of oxygen of at least 300 mm Hg, Dr. David L.S. Morales said at the annual meeting of the American Association for Thoracic Surgery.

As evidence to buttress this contention, Dr. Morales presented his analysis of more than 12,000 U.S. lung transplantations done during January 2000–November 2009, research that produced two unexpected findings.

First, throughout the decade, U.S. lung transplants with an arterial blood gas partial pressure of oxygen (Pao_2) of 300 mm Hg or less occurred in a surprisingly high 20% of all cases that had a documented Pao_2 level measured just before organ procurement. Lungs with a Pao_2 of 200 mm Hg or less were used in 5%-10% of all transplantations each year during 2000-2004, but the rate abruptly doubled in 2005, and during 2005-2009 the annual rate at which lungs with a Pao_2 of 200 mm Hg or less were used held fairly steady at about 20% of all lung replacement surgeries, said Dr. Morales, a heart surgeon at Baylor College of Medicine in Houston.

The second surprising finding from his analysis showed that transplant recipients who received a lung with a Pao_2 of 200 mm Hg or less had 1-year and 5-year graft survival rates that closely matched the rates among patients who received a lung with a Pao_2 of 201-300 mm Hg, those whose transplant registered a Pao_2 of 301-400 mm Hg, and even patients who received one or two lungs with a Pao_2 of more than 400 mm Hg. All four subgroups had 1-year survival rates of about 80% and 5-year rates of about 50%. In the subgroup that received lungs with the lowest Pao_2 levels (200 mm Hg or less), the 1-year graft survival rate was 82% and the 5-year graft survival was 53%, Dr. Morales reported.

In addition, a multivariate analysis that took into account 21 donor characteristics showed no statistically significant relationship between Pao_2 and graft survival.

"We are not saying that Pao_2 is not important when assessing a potential lung donor, but the level of importance seems [to be] less than previously believed," he said.

"Pao_2 is often the first [data item] a surgeon wants to know when considering lungs for transplant. [These findings] question why we established the criterion. The most important thing about my paper is that it calls the level of 300 mm Hg into question. If with further study we find that Pao_2 can be below that and graft survival is not affected, then perhaps we could increase the donor pool. I hope this paper will spur interest in looking at this" in another study, Dr. Morales said in an interview.

His study reviewed all U.S. lung transplants in the most recent 10-year period available, using data collected by UNOS (United Network for Organ Sharing). Of the 12,545 lung transplantations, records for 12,045 (96%) included information on the Pao_2 recorded just before the donor lung was taken for transplantation, so Dr. Morales focused his analysis on this group.

Dr. Morales said that he had no disclosures. ■

COMMENTARY

Dr. Joseph B. Barney, FCCP, comments: This is important and timely research, given the disparity between patients needing lung transplants and availability of acceptable organs. Many guidelines in existence are from experiences with the initial years of transplantation and are in need of review by scientific inquiry. Clearly we need a better, more comprehensive way of evaluating donor lungs. A larger, more prospective investigation is needed to decide if we need to fundamentally change the way we utilize available organs.

Specialty Not Filling Match Slots

Surgery • *from page 1*

medical graduates, and – most important of all – greater surgeon efficiency achieved through health care reform and intelligent reorganization of services, according to Dr. Grondin, a thoracic surgeon at the University of Calgary (Alta.), who has practiced in both Canada and the United States.

"One of the most striking differences, having worked on both sides of the fence, is that my city, Calgary, with a population of 1.3 million, has four hospitals. At one hospital we have four thoracic surgeons. We don't have competition with other hospitals. We're regionalized to one center, with no duplication of services. My name isn't up on a billboard saying that I'm the greatest thing since sliced bread. That's because the government controls how resources are allocated. It makes our system more efficient than the American system, from what I've seen," he said.

One of the reasons Dr. Grondin left Chicago and returned to Canada was that Northwestern University, where he practiced, grew from two hospitals to five in an effort to gain market share. He found himself spending hours every day driving from hospital to hospital.

"I was doing thoracic surgery at each hospital, basically to try to accommodate my pulmonologists. It was a completely inefficient model. The bottom line is, it's a lot better when surgeons bring their work in to one center as opposed to being on the road driving around and getting home at 8:00 at night. Now that I'm in one center, I have greater efficiencies clinically, research-wise, and I'm also more productive as an educator. I think that centralizing our services and not competing with the guy down the street are where the greatest efficiencies can be made," Dr. Grondin continued.

He took the "con" side of a structured debate on whether a manpower crisis in cardiothoracic surgery is looming by 2020. The "pro" side was advanced by Dr. Douglas J. Mathisen, immediate past president of the American College of Surgeons.

Dr. Mathisen cited several recent surveys that paint a disturbing picture of a profession in trouble: Cardiothoracic surgeons have the highest average age of any surgical specialty, it's projected that 73% of those now in practice will retire by 2019, women by and large continue to shun the field, and 28% of cardiothoracic surgeons describe themselves as somewhat or very dissatisfied with their work.

By one published estimate, in 15 years there will be 1,343 fewer cardiothoracic surgeons than needed to meet demand. Another estimate using a different methodology predicts a 39% shortage by the year 2030.

"There's an inexorable decline in applicants, especially in U.S. graduates of general surgery training programs. There has been a dramatic decline in interest in our specialty," said Dr. Mathisen, professor of surgery at Harvard Medical School and chief of the division of thoracic surgery at Massachusetts General Hospital, both in Boston.

In 2011 there are 72 cardiothoracic surgery training programs with 102 residency positions, down from 92 programs and 143 residency spots in 2002. Only 78 of the 102 residency positions in 2011 were filled in the match, and there were a mere 55 U.S. applicants for those spots.

"Virtually everybody who wants to be a cardiothoracic surgeon can at least enter a training program. There's very little selection process," he observed.

As a result, the quality of applicants is not what it used to be. And residents often emerge from their cardiothoracic surgery training less well prepared than in times past. Indeed, the failure rate on the oral board exam in 2011 was 34%, up sharply from an average of 15% during 1990-2006, Dr. Mathisen continued.

In contrast, the failure rate on the Canadian thoracic surgery board exam is about 5%, which is similar for the cardiac surgery exam. Unlike surgery in the United States, where most cardiothoracic surgeons do both cardiac and thoracic surgery, in Canada these specialties are completely separate. Thoracic surgery residents spend only 4-6 months on cardiac surgery, and cardiac surgery residents have 4-6 months of thoracic surgery. They take completely different board exams and don't share common professional meetings, Dr. Grondin said.

Audience members wanted to know if Canadian governmental regulation of health care and the centralization of services create lengthy waiting lists. Dr. Grondin said no. It takes an average of 7 days for him to see a lung cancer patient in his office from time of referral, and 3-4 weeks for the patient to get to the operating room.

"That's a little slower than when I was in Chicago, but well within the parameters identified for good outcomes," the surgeon added.

Session moderator Dr. Mark T. Metzdorff noted that the United States has 3.67 times more cardiothoracic surgeons per 100,000 population than Canada has.

"I think by any measure, Canada does a good job of cardiothoracic surgery with far fewer surgeons than in the United States, and in a similar geographic and maybe a similar demographic space," commented Dr. Metzdorff, a cardiothoracic surgeon in Denver.

Dr. Grondin said that despite the 3.67:1 per capita ratio of U.S. to Canadian cardiothoracic surgeons, Canadian surgeons aren't fretting about a possible manpower shortage by the decade's end. Just the opposite, in fact. In a recent national survey of Canadian thoracic surgery residents, 83% indicated there aren't enough jobs and 20% said they had extended their training due to the lack of jobs. A similar survey conducted among Canadian cardiac surgery residents found that 27% had extended their training due to a lack of jobs. That's the flip side of centralized services and maximized efficiency: It means fewer opportunities for young surgeons ready to start out in practice.

The speakers declared having no financial conflicts. ■

COMMENTARY

Dr. Richard Fischel, FCCP, comments: The numbers don't lie. Once considered one of the most competitive and highly respected professions to enter, cardiothoracic surgery in the United States is facing a very troubling future with significant implications for health care in our aging population. We should be very concerned that nationwide only 55 applicants applied for 102 residency spots in 2011. While consolidation of services such as that seen in the Canadian system may provide a beneficial model, we will still be in significant trouble if nobody wants to train in the field. This paper discusses an issue that should be front and center to every discussion about the future of medicine. We must act and act soon to address the problems in the residencies and the profession if we want any hope of quality cardiovascular and thoracic care when we will need it most.

Eplerenone Cut Events in Mild Heart Failure

BY PATRICE WENDLING
Elsevier Global Medical News

PARIS – The aldosterone antagonist eplerenone cut cardiovascular events and the need for hospitalization significantly across all risk levels in patients with mild heart failure, according to a subanalysis of the EMPHASIS-HF trial.

Eplerenone (Inspra) was also shown to trim troublesome and costly repeat heart failure hospitalizations in a subset of patients followed for up to 10 additional months after the pivotal, phase III trial closed, Dr. Bertram Pitt reported at the annual congress of the European Society of Cardiology.

"Overall efficacy, no matter where we looked, was about the same, and we had the same safety," Dr. Pitt told reporters.

EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) was stopped prematurely last spring after eplerenone in addition to standard therapy demonstrated a 37% (hazard ratio, 0.63) improvement over placebo in the primary end point of death from cardiovascular causes or heart failure hospitalization in 2,637 patients with mild New York Heart Association class II systolic heart failure (N. Engl. J. Med. 2011;364:11-21).

Among 1,597 patients who remained on double-blind therapy after study closure, the primary end point occurred in 21% on eplerenone and 29% on placebo (HR 0.66, *P* less than .0001), reported Dr. Pitt, of the University of Michigan in Ann Arbor.

Repeat hospitalization for heart failure was significantly reduced with eplerenone (rate ratio 0.62, *P* less than .001).

"This suggests, to us at least, that this is going to have important cost implications, quality of life implications, as well as important implications on survival, since we know that heart failure hospitalization relates to target-organ damage and survival," Dr. Pitt said.

The benefits of eplerenone were particularly compelling in elderly patients and those with diabetes and renal dysfunction, three high-risk populations in whom clinicians are hesitant to use adjuvant aldosterone blockade because of fears of inducing hyperkalemia, he said.

He pointed out that recent head-to-head data showed that the aldosterone antagonist spironolactone (Aldactone) increases hemoglobin A_{1c} and cortisol levels and reduces adiponectin in patients with diabetes, whereas eplerenone does not.

When Dr. Pitt and colleagues looked at patients with diabetes in the subanalysis, the benefit was better than that observed in the overall EMPHASIS-HF cohort, with a 46% reduction in the primary end point (HR 0.54, *P* less than .0001).

Dr. Pitt noted that the current American Heart Association, American College of Cardiology, and European guidelines for aldosterone blockade don't specify a particular agent, but look at the agents as a class.

"We believe with [these] data, that in the next guidelines there should at least be some consideration for the specific use of eplerenone, at least in the subset of patients with diabetes," he said.

Among patients with an estimated glomerular filtration rate less than 60 mL per minute per 1.73 m^2, the improvement in the primary outcome reached 38% with eplerenone over placebo (HR 0.62, $P = .0001$).

The study excluded patients with a baseline serum potassium level above 5.0 mmol/L and estimated GFR below 30 mL per minute per 1.73 m^2 in an attempt to minimize the risk of hyperkalemia.

Despite this, the positive results remain applicable, Dr. Pitt said in an interview.

Among elderly patients at least

COMMENTARY

Dr. Jun Chiong, FCCP, comments: Aldosterone antagonists have consistently shown a mortality benefit among patients with systolic heart failure. With data like these, this should be part of the core measures in heart failure just like ACE inhibitors and ARBs.

75 years old, the benefit on the primary end point with eplerenone reached 34% (HR 0.66, *P* = .004).

Significant benefits were also observed in patients with a left ventricular ejection fraction less than 30% (HR 0.65, *P* less than .0001) and with a median systolic blood pressure less than 123 mm Hg (HR 0.63, *P* less than .0001).

As seen in the overall EMPHASIS-HF cohort, the benefits of eplerenone were accompanied by a significant increase in the incidence of serum potassium more than 5.5 mmol/L in each of the high-risk subgroups.

There were, however, no significant increases in the incidence of serum potassium more than 6 mmol/L, hospitalization leading to treatment discontinuation, hospitalization for/or deaths due to hyperkalemia, or hospitalization for worsening renal function, Dr. Pitt said.

This is going to have important cost, quality of life, and survival implications.

DR. PITT

Invited discussant Dr. Piotr Ponikowski, of the 4th Military Hospital in Wroclaw, Poland, highlighted as important the benefits of eplerenone in people with diabetes and the reduction in repeat hospitalizations.

Dr. Ponikowski noted that up to 50% of heart failure patients are rehospitalized and these visits are associated with significant costs, reduced quality of life, and mortality.

Still, aldosterone antagonists remain underutilized in heart failure patients throughout Europe as well as the United States, he said.

Physicians frequently question whether clinical trial data are real, consistent, and clinically meaningful, he said. "With the presented data, we can now say that the answer to all these questions is 'yes.' "

Pfizer sponsored the trial. Dr. Pitt reported financial relationships with several firms excluding Pfizer. His coauthors reported similar relationships including employment with Pfizer. ■

Algorithm Helps Tell MI From Noncoronary Disease

BY SHERRY BOSCHERT
Elsevier Global Medical News

PARIS – A new algorithm incorporating high-sensitivity cardiac troponin T values in patients with ST-segment elevation seems to differentiate between MI and cardiac but noncoronary disease in patients with acute chest pain.

The algorithm could help triage patients in the first hour of presentation so that the patients who need coronary angiographies get them quickly and unnecessary angiographies are minimized, Dr. Philip Haaf said in a press briefing at the annual congress of the European Society of Cardiology.

Troponins are increased in cardiovascular disorders including tachyarrhythmia, heart failure, hypertensive urgency or emergency, Takotsubo cardiomyopathy, and myocarditis in patients without a coronary obstruction. The introduction of high-sensitivity assays for cardiac troponins has allowed earlier diagnosis of acute MI in many patients.

But the assays also have caused "considerable confusion among treating physicians" because minor elevations in cardiac troponins can be seen in some patients who do not have a coronary obstruction but have tachyarrhythmia, hypertensive urgency, or heart failure, said Dr. Haaf of University Hospital Basel (Switzerland).

He and his associates analyzed data on the first 887 patients who presented with acute chest pain in the APACE (Advantageous Predictors of Acute Coronary Syndrome Evaluation) study. The ongoing, multicenter study has enrolled close to 2,000 patients so far, obtaining a meticulous patient history, ECG analysis, and measures of novel cardiac biomarkers from each. High-sensitivity cardiac troponin T (hs-cTnT) was measured at presentation and serially thereafter in a blinded fashion; final diagnosis was adjudicated by two independent cardiologists.

They found that the initial hs-cTnT value and the absolute change in hs-cTnT value within the first hour helped differentiate MI from cardiac but noncoronary disease but that the relative change in hs-cTnT was less discriminatory. In a receiver operating characteristic analysis, using both the initial hs-cTnT and absolute change in the first hour provided an area under the curve of 0.94.

THE ALGORITHM COULD HELP PATIENTS WHO NEED CORONARY ANGIOGRAPHIES GET THEM QUICKLY AND MINIMIZE UNNECESSARY ANGIOGRAPHIES.

"This is all statistics. What we tried to do is translate these statistics into more clinically applicable terms," Dr. Haaf said.

Analyzing data on 127 patients with acute MI and 125 with cardiac, noncoronary disease, they found that in the 233 patients with ST-segment elevation on ECG, 98% of patients who had an MI had either presentation values for hs-cTnT above 0.028 mcg/L or an absolute change in hs-cTnT of at least 0.005 mcg/L in the first hour.

Changes in hs-cTnT after the first hour did not add much helpful information, he added.

This three-step algorithm – ST elevation, hs-cTnT value at presentation, and absolute change in hs-cTnT in the first hour – provided a positive predictive value of 79% and a "relatively high" negative predictive value of 98% in differentiating acute MI from cardiac, noncoronary disease, Dr. Haaf said.

The study was funded by the Swiss National Science Foundation, the Swiss Heart Foundation, Abbott, Roche, Nanosphere, Siemens, and University Hospital. No disclosures were reported. ■

COMMENTARY

Dr. Jun Chiong, FCCP, comments: This will help cardiologists and ED specialists sort out elevated troponin, as troponin is simply indicative of myocardial injury. It's up to the clinician to determine if the cause is coronary.

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

Decreased Sperm Counts

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

Decreases in Hemoglobin and Hematocrit

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

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

A decrease in hemoglobin concentration by at least 1 g/dL was observed in 57% of bosentan-treated patients as compared to 29% of placebo-treated patients. In 80% of those patients whose hemoglobin decreased by at least 1 g/dL, the decrease occurred during the first 6 weeks of bosentan treatment. During the course of treatment the hemoglobin concentration remained within normal limits in 68% of bosentan-treated patients compared to 76% of placebo patients. The explanation for the change in hemoglobin is not known, but it does not appear to be hemorrhage or hemolysis.

Pulmonary Veno-Occlusive Disease

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

Prescribing and Distribution Program for Tracleer

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

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

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

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

ADVERSE REACTIONS

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

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

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

Clinical Studies Experience

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

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

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

The adverse drug events that occurred in ≥3% of the bosentan-treated patients and were more common on bosentan in placebo-controlled trials in pulmonary arterial hypertension at doses of 125 or 250 mg twice daily are shown in Table 2:

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

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

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

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

Postmarketing Experience

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

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

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

DRUG INTERACTIONS

Cytochrome P450 Summary

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

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

Hormonal Contraceptives

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

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

Cyclosporine A

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

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

Glyburide

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

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

Infarct Size Not Reduced With Balloon Therapy

BY PATRICE WENDLING
Elsevier Global Medical News

PARIS – Intra-aortic counterpulsation balloon therapy during percutaneous coronary intervention did not reduce infarct size in patients with ST-elevation MI without shock in the multicenter, international CRISP-AMI trial.

The findings do not, however, close the door on this widely used therapy, Dr. Manesh Patel said.

"Clinicians should continue to be vigilant about identifying patients who are at risk for rapid deterioration or hypertension that may still benefit from support, as seen with the crossover in this trial," he said at the annual congress of the European Society of Cardiology.

In all, 8.5% of patients randomized to percutaneous coronary intervention (PCI) alone crossed over to rescue intra-aortic balloon counterpulsation (IABC) in the CRISP-AMI (Counterpulsation to Reduce Infarct Size Pre-PCI Acute Myocardial Infarction) study (JAMA 2011;306:1329-37).

Among all 337 patients in the trial, mean infarct size was 42% of the left ventricle in patients randomized to IABC prior to PCI and continued for at least 12 hours and 37.5% in the PCI-alone group ($P = .06$), said Dr. Patel of the Duke Clinical Research Institute in Durham, N.C.

In patients with proximal left anterior descending and thrombolysis in myocardial infarction flow scores of 0 or 1, the mean infarct size was 46.7% of the left ventricle vs. 42.3%, respectively ($P = .11$).

Invited discussant Dr. Kurt Huber, director of the department of medicine, cardiology, and emergency medicine at Wilhelminenspital in Vienna, said, "I'm sure that this method is still important for certain patient groups."

At 6 months, three patients in the IABC plus PCI group had died vs. nine in the PCI-alone group ($P = .12$).

An exploratory composite end point of time to death, shock, or new or worsening heart failure also favored the counterpulsation therapy plus PCI group over the PCI-alone group (8 vs. 21 events, $P = .03$). There was a nonsignificant rise in side effects, particularly vascular complications.

At 30 days, major vascular complications occurred in seven patients in the IABC plus PCI group vs. only two in the PCI-alone group ($P = .09$.). Major bleeding or transfusion occurred in five patients vs. three patients, respectively, Dr. Patel reported.

Dr. Huber said other studies are needed to define which patients might benefit from IABC. He highlighted the only other prospective trial of IACP, the TACTICS trial, in which IAPC failed to offer a survival benefit when added to fibrinolysis for patients with MI who were hemodynamically unstable, but suggested a possible benefit for patients with the most severe heart failure or hypertension (J. Thromb. Thrombolysis 2005;19:33-9).

Session comoderator Dr. Christodoulos Stefanadis of Athens University Medical School said in an interview that it is still acceptable to use IACP in both stable and unstable patients, but agreed that other studies are needed to resolve the issue.

"In unstable patients, I personally believe that the use of the intra-aortic pump remains effective, but the question is what happens in stable patients without low blood pressure or shock."

At baseline, CRISP-AMI patients were hemodynamically stable, with a median systolic blood pressure of 130 mm Hg in the IABC plus PCI group and 135 mm Hg in the PCI-alone patients.

The time required to insert the intra-aortic balloon added just 9 minutes to the procedure, making it unlikely that this derailed the potential benefits of counterpulsation therapy, Dr. Patel said in an interview.

Dr. Patel reported receiving grant funding and travel reimbursement from the study sponsor Maquet. ■

COMMENTARY

Dr. Jun Chiong, FCCP, comments: The outcome is quite a surprise. This is also why we need to be reminded that randomized trials are the gold standard in evidence-based medicine. Another clinical trial called SHOCK, presented 4 years ago, also had neutral results. However, subanalyses have to be done to determine the fraction of patients who will strongly benefit.

Novel Drug Reduced VTE Events During Chemotherapy

BY RICHARD HYER
Elsevier Global Medical News

CHICAGO – Prophylaxis with semuloparin, an experimental ultralow-molecular-weight heparin, achieved a significant 64% reduction in relative risk for venous thromboembolism events among cancer patients undergoing chemotherapy in a large, randomized, double-blind, phase III trial called SAVE-ONCO.

An intent-to-treat analysis found that the rate of VTE events – a composite of symptomatic deep vein thrombosis, any pulmonary embolism, and VTE-related death – was 1.2% in patients treated with semuloparin vs. 3.4% in a control group treated with placebo (hazard ratio, 0.36; *P* less than .0001).

Benefits trended in favor of semuloparin for all components of the composite end point, including any pulmonary embolism (odds ratio, 0.41) and VTE-related death (OR, 0.77), reported Dr. Daniel J. George, who presented the paper on behalf of Dr. Giancarlo Agnelli of Perugia (Italy) University at the annual meeting of the American Society of Clinical Oncology.

Although the incidence of clinically relevant bleeding was higher at 2.8% with semuloparin vs. 2% for placebo, Dr. George added that a safety analysis found the incidence of major bleeding was similarly low, at 1.2% and 1.1%, respectively.

Based on the trial results, Dr. Elias Zerhouni, president of global research and development at trial sponsor Sanofi-Aventis, announced that the company plans "to submit semuloparin for regulatory filing" in the third quarter of 2011. Still investigational, the selectively engineered anticoagulant has high anti–coagulation factor Xa activity and minimal anti–coagulation factor IIa activity with a half-life of 16-20 hours.

Although it is advocated for cancer patients who are hospitalized or undergoing surgery and is not contraindicated for anticoagulation, routine prophylaxis of ambulatory cancer patients on chemotherapy is not currently recommended.

"So this leaves us with the question, Which cancer patients should we now consider for thromboprophylaxis?" said Dr. George of Duke University Medical Center in Durham, N.C. "Already our guidelines suggest that those patients with cancer undergoing major surgery, or hospitalized, or acutely ill, ought to be anticoagulated with low-molecular-weight heparin during those periods of time.

"I would now submit that the SAVE ONCO data would support having patients initiating chemotherapy, in the setting of locally advanced or metastatic disease, as a third population that we could consider for thromboprophylaxis."

Although discussant Dr. Vered Stearns of Johns Hopkins University in Baltimore viewed the findings favorably, she cautioned that "SAVE-ONCO should not change current practice for the overall population."

Dr. Stearns emphasized that predictive models are needed to determine which ambulatory patients are at the highest risk for VTE, "and who should be offered prophylaxis in the context of expected clinical outcomes." Biomarkers such as circulating coagulating factors are also important, she added. "My understanding is [that] the group is conducting subgroup analysis and evaluation of predictive markers that may help us select the population that would benefit from primary prophylaxis."

A multinational study, the SAVE-ONCO trial enrolled 3,200 patients who were at high risk of VTE. Participants had metastatic or locally advanced solid tumors for which they were starting a new course of chemotherapy with minimum treatment intent of 3 months.

Patients were randomized 1:1 to standard-care chemotherapy plus either placebo or semuloparin 20 mg subcutaneously once daily for the length of their chemotherapy.

Patient median age was 60 years, and 60% of patients were men. More than two-thirds had metastatic disease. Lung cancer was the most common tumor type (36%) followed by colon/rectal cancer (28%). The remainder had cancer of the stomach, ovary, pancreas, or bladder. Treatment duration was approximately 3.5 months in both groups.

In response to audience questions, Dr. George said that the study did not show a survival benefit, but "there is likely a subset of patients" for whom this made a dramatic impact in their early morbidity and mortality.

The study did not address cost, but that will be a factor if prophylaxis is introduced for a large population of cancer patients, he acknowledged.

The study was sponsored by Sanofi-Aventis. Dr. George disclosed numerous relationships with pharmaceutical companies, including Sanofi-Aventis. Dr. Agnelli disclosed receiving honoraria from Sanofi-Aventis and relationships with other companies. Dr. Stearns disclosed honoraria and research funding from other companies. ■

COMMENTARY

Dr. W. Michael Alberts, FCCP, comments: This study documents a small but significant reduction in risk for VTE events in patients undergoing chemotherapy who receive the active drug. The key question now, as listed in the article, is "which cancer patients should we now consider for thromboprophylaxis?" Additionally, the study did not address cost. This factor will no doubt be important as indications for the use of semuloparin are developed.

Adjuvant Colchicine Halves Pericarditis Recurrences

BY PATRICE WENDLING
Elsevier Global Medical News

PARIS – In patients with a first recurrence of pericarditis, adding low-dose colchicine to standard therapy halved the risk of subsequent episodes.

Among 120 patients with a first recurrence of pericarditis in the Study of Colchicine to Treat and Prevent Recurrent Pericarditis (CORP) trial, the rate at 18 months of another recurrence was 24% with colchicine and standard therapy and 55% with placebo and standard therapy (*P* less than .001).

The relative risk reduction associated with adjuvant colchicine was 56% and the number needed to treat to prevent one recurrence was three, Dr. Massimo Imazio reported at the annual congress of the European Society of Cardiology.

Colchicine (Colcrys) has been used for years to treat gout and is the first drug to be shown in a double-blind, randomized, placebo-controlled trial to prevent recurrent pericarditis.

"Following an initial episode of recurrent pericarditis, colchicine, as an adjunct to anti-inflammatory therapy, appears to be an inexpensive and safe means to hasten symptom resolution, improving remission rates by 1 week, and to reduce further recurrences," said Dr. Imazio of the Maria Vittoria Hospital in Turin, Italy.

Invited discussant Dr. Andre Keren, of the Heart Institute at Hadassah University Hospital in Jerusalem, described CORP as a well-designed and carefully performed trial. Its results strongly support the use of low-dose colchicine in pericarditis patients.

"I really believe that the time has arrived that colchicine should be more freely used," he said.

Both Dr. Imazio and Dr. Keren observed that the results may not be applicable to all patients with pericarditis since the trial excluded those with neoplastic or bacterial etiologies as well as those with multiple recurrences.

In addition, the drug's "remarkable" safety and tolerability profile might have been influenced by careful patient selection and the low doses used in the study, Dr. Keren said.

Based on nonrandomized observational findings and expert opinion, the European Society of Cardiology guidelines recommend colchicine 2 mg/day for 1-2 days, followed by a maintenance dose of 1 mg/day for recurrent pericarditis.

The CORP investigators randomized patients from four Italian centers to conventional therapy plus placebo or colchicine for 6 months at the recommended doses for patients weighing at least 70 kg, but reduced the initial dose to 1 mg/day and the maintenance dose to 0.5 mg/day for those weighing less than 70 kg.

Conventional therapy was aspirin 800-1,000 mg or ibuprofen 600 mg every 8 hours for 7-10 days, with the second choice being prednisone 0.2-0.5 mg/kg of body weight per day for 4 weeks and then gradually tapered.

Dr. Keren pointed out that the dose as well as the frequency of corticosteroids was lower in CORP than the researchers' earlier CORE trial, in which prednisone was dosed at 1.0-1.5 mg/kg of body weight per day for 4 weeks, and 35% of patients had received steroids during the initial episode of pericarditis. In contrast, only 10% of placebo and 8% of colchicine patients in CORP had previously received corticosteroids.

"This might also reflect, in my view, a change in our perception that steroids can actually be deleterious in decreasing the recurrence rate," Dr. Keren said.

Symptom persistence at 72 hours was significantly lower in the colchicine group than in the placebo group (23% vs. 53%, *P* = .001), as was the rate of remission at 1 week (48% vs. 82%, *P* less than .001), Dr. Imazio said.

The mean number of recurrences was significantly lower in the colchicine-treated group than in the placebo group (0.1 vs. 1.0), and the time to first recurrence was also significantly longer at 2.5 months vs. 1 month (both *P* less than .001).

No significant differences were observed between the two groups in rates of readmission (5% vs. 13%), tamponade (0% vs. 2%), or constriction (0% both).

Gastrointestinal intolerance was the most common side effect, reported in four colchicine and five placebo patients. No severe side effects were observed in either group. Treatment discontinuation occurred in five colchicine and four placebo patients, Dr. Imazio said.

Full results of CORP are available online in the Annals of Internal Medicine (2011 Aug. 28 [Epub ahead of print]).

Dr. Imazio and his coauthors report no study sponsorship or conflicts. Dr. Keren reports no disclosures. ■

COMMENTARY

Dr. Jun Chiong, FCCP, comments: Colchicine has long been known to be useful in the treatment of pericarditis. However, the use of NSAIDs is still more popular. With the graying of America, the risk of renal failure is high among patients who have to take a high-dose NSAID. It is very helpful to know that a safer agent can be used for acute pericarditis.

Are Benchmarks the Problem for High VAP Rates?

'It is not appropriate to measure all trauma centers against a single benchmark.'

BY RICHARD M. KIRKNER
Elsevier Global Medical News

CHICAGO – Payers are relying ever more on tying physician and hospital payments to quality measures, but what happens if the benchmarks they use vary among institutions or are flawed? Such may be the case with ventilator-associated pneumonia and large trauma centers, as a recent study shows VAP rates at such facilities exceed national benchmarks, which some say are inadequate for comparison.

Dr. Christopher P. Michetti of Inova Fairfax Hospital in Falls Church, Va., presented a retrospective study designed to determine VAP rates at major trauma centers and to lay groundwork for more accurate benchmarking that relies less on National Health Safety Network data, he said. He spoke at the annual meeting of the American Association for Surgery in Trauma. The study was performed through the AAST Multi-Institutional Trials Committee.

"Hospitals are under pressure to reduce their VAP rates, yet a direct association between VAP rates and quality of care or outcomes has not been demonstrated," he remarked.

"VAP rates … are remarkably variable," Dr. Michetti said. "It is not appropriate to measure all trauma centers against a single benchmark, nor does an actual benchmark appear to exist at this point." Comparing VAP rates between different trauma centers is "like comparing apples and oranges," he said.

The study looked at VAP rates at 47 level I and II trauma centers for 2008 and 2009 with an average of 3,000 trauma evaluations a year. The average VAP rate for the study group was 17.2/1,000 ventilator days, compared with 8.1/1,000 for NHSN data. "In fact, the 90th-percentile rate for NHSN was still below the mean rate from our study," Dr. Michetti said. Across all 47 centers in the study, VAP rates ranged from a low of 1.8/1,000 ventilator days to a high of 57.6/1,000 ventilator days.

The case mix at the trauma centers did not auger well for lower VAP rates, as 88% of the cases were blunt trauma, Dr. Michetti noted. "VAP rates are generally higher for blunt-trauma patients, at about 17/1,000 ventilator days, compared with penetrating trauma at 11/1,000," he said.

Most other variables among the centers in the study – such as having a closed or open ICU, or using a bacteriologic vs. a clinical strategy to diagnose VAP – showed little impact on the pneumonia rates. VAP rates did not correlate with the size or level of trauma center, injury severity, or type of ICU, he said.

Among the problems he noted with the NHSN data on VAP rates are the lack of source hospital identification, population risk, or injury severity stratification. "In addition, the NHSN rates are substantially lower than other published rates among trauma patients," he said.

However, the investigators did isolate a few variables that may influence VAP rates: Among centers where the trauma service alone made the diagnosis, the average VAP rate was 27.5/1,000 ventilator days. When the infection control, quality, or epidemiology department made the call, the average VAP rate was 11.9/1,000 days. Centers that excluded patients also had rates about 30% lower than those that did not. This variability raises questions about using VAP as a quality measure, Dr. Michetti said. "Before we take that leap, diagnostic and reporting standards are necessary."

The heightened attention on VAP as a quality measure for critical care is having other implications, he said. "As pressure to reduce VAP rates grows, an increasing number of patients are being labeled as having ventilator-associated tracheobronchitis or excluded for reasons such as aspiration," he said.

Discussant Dr. Karen J. Brasel of the Medical College of Wisconsin, Milwaukee, acknowledged the need for the study, but raised the question: "Are the benchmarks the problem, or are we the problem?"

"I think the answer is yes, both," Dr. Michetti said. "I'm not sure that an adequate benchmark exists probably because no representative sample of trauma centers has been done to set that benchmark." He noted that the CDC's Healthcare Infection Control Practices Advisory Committee does not recommend reporting of VAP, which argues against using that as a benchmark. Meanwhile, across individual centers no reporting standards exist, "so centers can't agree on what is VAP," he said. ■

VITALS

Major Finding: AAST study shows major trauma centers have higher VAP rates than do national benchmark data.

Data Source: Retrospective analysis of trauma admissions at 47 level I and II centers sponsored by the AAST Multi-Institutional Trials Committee.

Disclosures: Dr. Michetti had no disclosures, and the study received no outside funding.

COMMENTARY

Dr. Marcos Restrepo, FCCP, comments: This study enhances the concerns of using VAP as a benchmarking tool, especially in the trauma population where "one size clearly does not fit all." In addition, there is a possible association of having trauma patients intubated in the field and developing VAP as a risk factor, which is difficult to control for. Information regarding the different interventions used in the participating centers to prevent VAP and how their compliance may have influenced the numbers might be very important at the time of interpreting the data. It is very important to have these type of studies in order to better understand how VAP or hospital-acquired respiratory infections can be prevented and, more importantly, protect our patients' safety.

VAP Rates Comparison

	Study period	No. of centers	Ventilator days	No. of patients with VAP	VAP rate per 1,000 ventilator days
NHSN Data	2006-2008	41	145,294	1,173	8.1
AAST Study	2008-2009	47	165,283	2,844	17.2

Elsevier Global Medical News

Pneumonia Hospitalization Risk Higher in ESRD Patients

BY SUSAN LONDON
Elsevier Global Medical News

CHICAGO – Patients with end-stage renal disease have sharply elevated rates of hospitalization for pneumonia throughout the renal transplantation trajectory, researchers reported at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy.

The findings underscore the importance of vaccinating this group against pneumococcal and other diseases, lead investigator Lise Haubjerg Nielsen said in an interview. Pneumonia "is a big economic burden for society and it is a huge [source of] mortality for these patients."

In a Danish nationwide population-based cohort study among more than 90,000 individuals, those with end-stage renal disease (ESRD) had an 8- to 14-fold higher incidence of such hospitalization, depending on whether they were wait-listed, post transplant, or post graft failure, when compared with their counterparts in the general population.

About one-third of the post-transplant group was hospitalized for pneumonia. Male sex and older age were among the significant risk factors for pneumonia hospitalization at this stage. On the other hand, risk fell after the first year post transplant.

The marked increase in post-transplant risk was expected, given patients' use of immunosuppressants, according to Ms. Nielsen, who is a medical student undertaking a research year in the department of infectious diseases at Aarhus University Hospital, Skejby.

However, the fact that the elevations seen before and after transplantation were even greater was surprising, she said at the meeting, which was sponsored by the American Society for Microbiology.

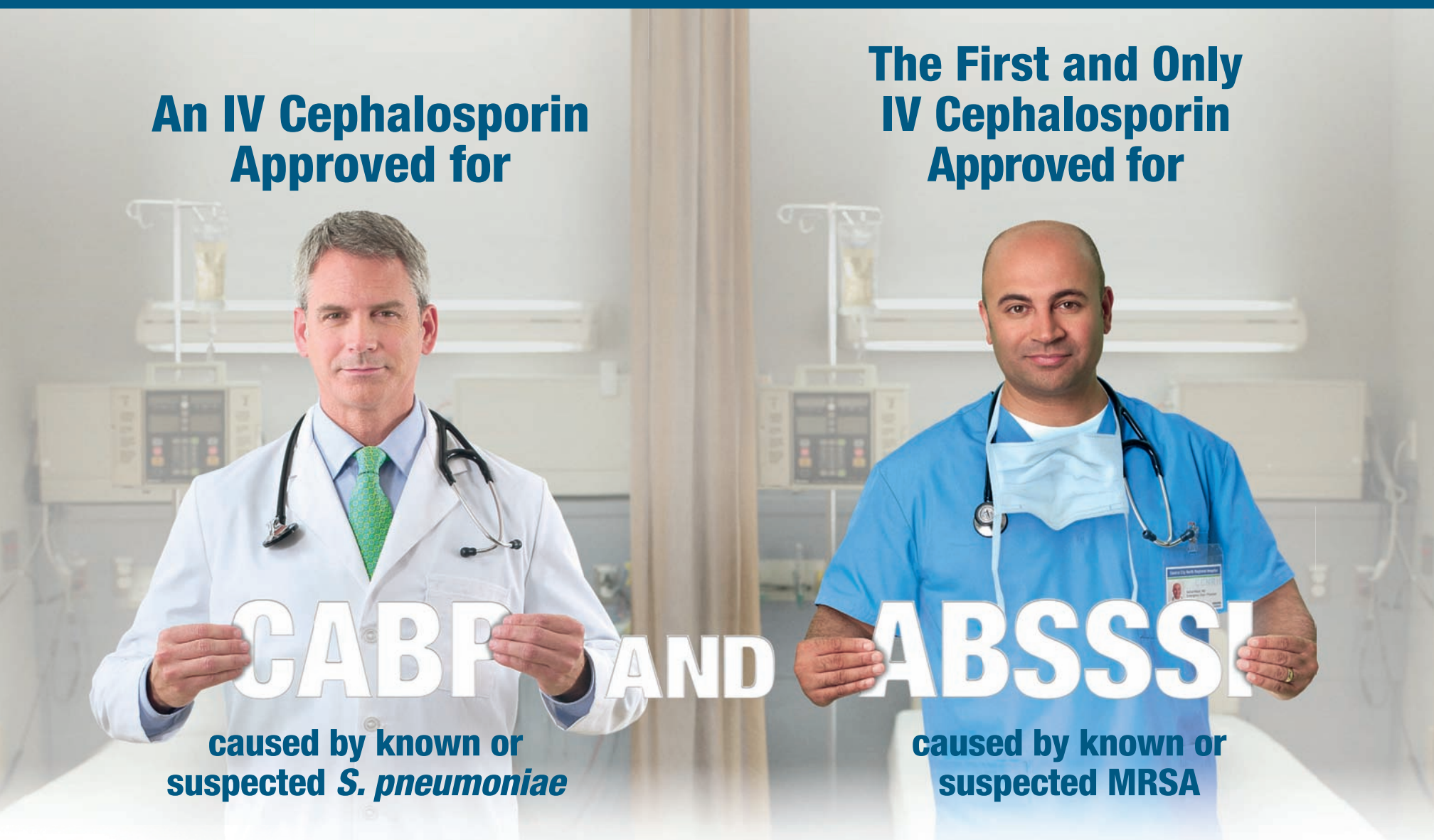
The increase in pretransplant risk was probably caused by patients' uremic state, while that post–graft failure "could also be just [a reflection of] these patients being more sick than the general population," she speculated.

The investigators analyzed data from the Danish National Hospital Registry, identifying all hospitalizations since 1977 having a discharge diagnosis of pneumonia, regardless of whether the infection was community or hospital acquired. They assessed first hospitalizations for pneumonia (excluding those caused by *Pneumocystis jiroveci*) occurring during 1990-2009. Patients with ESRD who were wait-listed for and/or underwent transplantation were matched by age and sex with up to 19 unaffected individuals from the general population. Analyses were based on 4,973 individuals with and 85,899 individuals without ESRD.

The incidence of first pneumonia hospitalization was 46, 32, and 63 per 1,000 person-years among wait-listed patients, renal transplant recipients, and patients who experienced graft loss, respectively.

These groups had corresponding 10-, 9-, and 14-fold increases in the incidence of such hospitalization compared with the general population, according to Ms. Nielsen.

Ms. Nielsen reported that she had no relevant conflicts of interest. ■



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 CABP or ABSSSI that are proven or strongly suspected to be caused by susceptible bacteria.**
- **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.**

INDICATIONS

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

IMPORTANT SAFETY INFORMATION

Contraindications

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

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

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

Teflaro®
(ceftaroline fosamil) for injection
600 mg • 400 mg

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

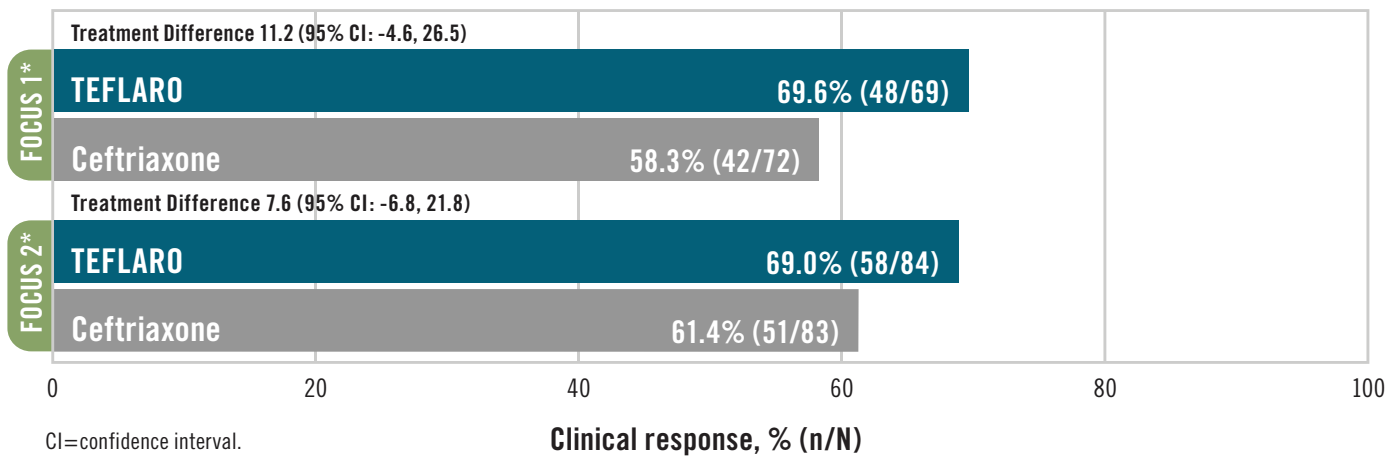
Adverse Reactions

- 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]

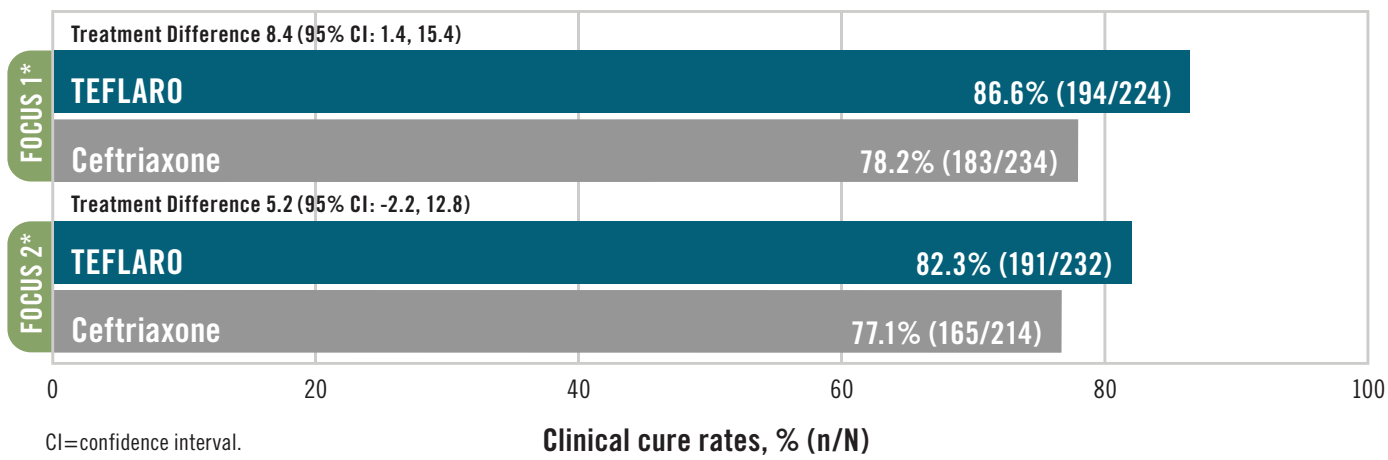


CI=confidence interval.

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

CABP

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



CI=confidence interval.

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

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

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

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

IMPORTANT SAFETY INFORMATION

Drug Interactions

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

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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.

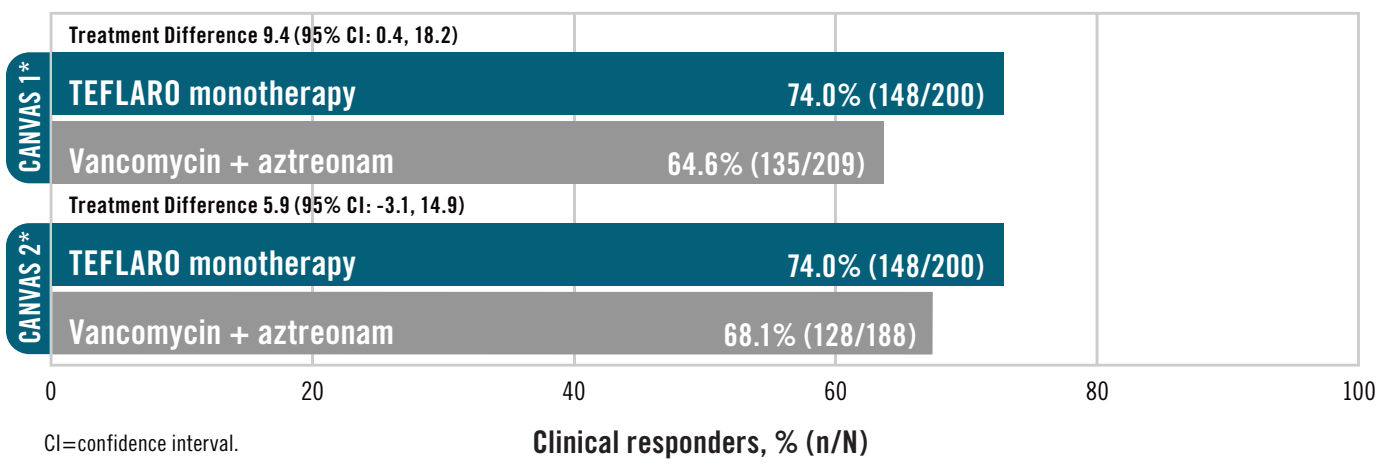
IMPORTANT SAFETY INFORMATION

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]



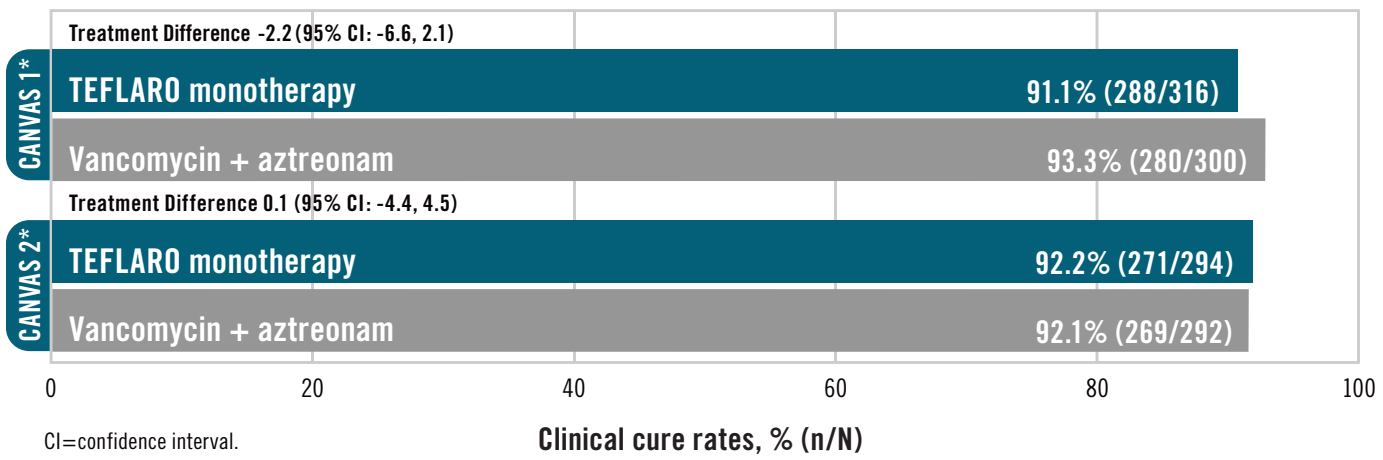
CI=confidence interval.

Clinical responders, % (n/N)

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.

Clinical cure rates, % (n/N)

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

*CANVAS=**C**eft**a**rolin**e** **v**s **V**a**n**comycin 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.

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

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.

Forest Pharmaceuticals, Inc.
Subsidiary of Forest Laboratories, Inc.
St. Louis, Missouri 63045

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Profiteers Taking Advantage of Drug Shortages

BY MARY ELLEN SCHNEIDER
Elsevier Global Medical News

A gray market of secondary pharmaceutical suppliers is driving up the price of lifesaving drugs that are in short supply, with markups ranging from 100% to 4,500%.

An analysis released by the Premier Healthcare Alliance found that, on average, drugs are being marked up 650% on the gray market. Premier compiled and analyzed 636 unsolicited sales offers received by acute care facilities in its network. All of the drugs offered were either back-ordered or unavailable through the manufacturer. While the average markup for these drugs was 650%, the top 10 highest markups were more than 1,000% over base contract prices.

The top 10 highest markups were seen in pharmaceuticals used in cardiology, sedation, critical care, and oncology:

- Labetalol – 4,533%
- Cytarabine – 3,980%
- Dexamethasone 4-mg injection – 3,857%
- Leucovorin – 3,170%
- Propofol – 3,161%
- Papaverine – 2,979%
- Protamine sulfate– 2,752%
- Levophed – 2,642%
- Sodium chloride concentrate – 2,350%
- Furosemide injection – 1,721%

Gray market vendors generally advertise drugs through e-mails and faxes that tout the shortage of the products, Premier officials said, with language such as "we only have 20 [units] of this drug left and quantities are going fast."

The reported price gouging comes as the country faces an unprecedented shortage of drugs. By the end of 2011, there could be more than 360 drugs in short supply, according to projections by Premier.

Hospitals and pharmacies must beware when purchasing drugs on the gray market, not just because of the inflated price, but also because of safety risks, Premier officials warned. Products sold on the gray market may have been mishandled, rendering them ineffective or harmful; they also could be counterfeit or diluted.

NO ONE WANTS 'A LITTLE KID DYING BECAUSE HE DOESN'T GET A CANCER DRUG BECAUSE WE HAVEN'T BEEN ABLE TO FIGURE OUT THE BUREAUCRACY.'

Stolen, counterfeit, and mishandled drugs are also difficult to recognize. Even the original manufacturers may not be able to spot fake drugs, according to analysts for Premier. And hospitals that try to avoid gray market vendors may encounter problems because these vendors have sophisticated methods of impersonating legitimate, licensed distributors, according to Premier.

Drug shortages are also getting increased attention in Washington, where a bipartisan group of senators has been urging the Food and Drug Administration to do more to address these shortages. The FDA held a public workshop on the issue on Sept. 26, where increased communication among stakeholders was called for (www.fda.gov/Drugs/NewsEvents/ucm265968.htm).

Sen. Amy Klobuchar (D-Minn.), a member of the bipartisan group, told reporters that one short-term solution would be for drug manufacturers to alert the FDA to any problems that could result in a drug shortage; she is sponsoring a bill (S. 296, the Preserving Access to Life-Saving Medications Act) that would require manufacturers to do so.

This would allow the FDA to begin looking across the United States and overseas for alternative drugs before a shortage occurs, Sen. Klobuchar said, adding that a range of options needs to be on the table to address drug shortages and the price gouging coming from the gray market.

"I don't care how much fighting is going on in Congress," she said. "I don't think anyone wants to be responsible for a little kid dying because he doesn't get a cancer drug because we haven't been able to figure out the bureaucracy of this." ■

Frequent Use of CPOE Shown to Save Lives

BY MARY ELLEN SCHNEIDER
Elsevier Global Medical News

Current government thresholds for the "meaningful use" of computerized provider order entry in the hospital may not be high enough to actually save lives, according to a simulation conducted by researchers at the Rand Corporation.

The researchers estimated the impact on mortality in a sample of more than 2,500 hospitals using computerized provider order entry (CPOE) for 26%-50% of patients, and found that that level of use could reduce mortality for heart failure and acute MI among hospitalized Medicare beneficiaries by 1.2% – not a statistically significant reduction.

But a second simulation found that mortality could be significantly reduced (2.1%) if CPOE were used for 51%-90% of patients hospitalized for those conditions (Health Affairs 2011 Sept. 14; doi:10.1377/hlthaff.2011.0245).

The results could help influence policy makers as they set standards for the later stages of the electronic health records (EHR) incentive program, the authors noted. The program was authorized by Congress in the 2009 Health Information Technology for Economic and Clinical Health (HITECH) Act and will provide about $27 billion in payments to physicians, hospitals, and other providers by the end of 2016.

Under stage 1 of the program, hospitals are required to use CPOE on medication orders for at least 30% of their eligible patients; under initial regulations governing the program, the threshold could rise to 60% in stage 2 and 80% in stage 3 of the program.

However, even the initial requirements for CPOE have been criticized by health care providers as being too strict. And recently, the Health Information Technology Policy Committee convened by the Health and Human Services department to help implement the incentive program recommended delaying the implementation of stage 2 requirements by a year.

The Rand study results could be ammunition for policy makers seeking to make the program more robust. "Our study should reassure policy makers at HHS and other stakeholders that high levels of use of computerized provider order entry and other health information technology have value and are likely to yield tangible health benefits for patients," Spencer S. Jones, an associate information scientist at Rand in Boston and lead author of the study, said in an interview.

But Mr. Jones added that there is currently no research setting out the optimal pace for EHR adoption. While proceeding at a cautious pace may be an appropriate strategy, maintaining parallel paper and electronic systems could lead to unintended adverse consequences, he said.

The study, which relied on data from 2,543 privately owned general acute hospitals, also compared the impact of any use of CPOE to no use and found that hospitals that used CPOE even a small amount achieved lower mortality rates for heart failure, acute MI, and pneumonia among Medicare beneficiaries. However, when the researchers adjusted for potential confounding factors that might affect mortality, there was a statistically significant relationship between CPOE use and lower mortality only for acute MI and heart failure. It could be that CPOE is more helpful in reducing medication errors for such complex chronic conditions as heart failure than for acute conditions like pneumonia, the researchers wrote.

The researchers analyzed data from the 2007 American Hospital Association annual survey database and the AHA's Information Technology Supplement from the same year. Mortality data are from the CMS's Hospital Compare database.

The researchers disclosed no conflicts of interest. The study was funded by philanthropic contributions from members of the Rand health board of advisers. ■

COMMENTARY

Dr. Jeana O'Brien, FCCP, comments: This study by the Rand Corporation supports the previous evidence regarding the mortality benefit to patients through use of CPOE. While institutions and care providers ultimately need to move to complete use of CPOE, there must also be time to safely develop processes around handling of the electronic orders and ensuring appropriate technology training and safeguards. It is almost certain the later stages of meaningful use will require high levels of CPOE use. The pace at which this occurs must take into consideration the operational details and magnitude of CPOE, as well as the impact of other simultaneous meaningful use requirements.

Medicare to Begin Testing Bundled Payments

BY MARY ELLEN SCHNEIDER
Elsevier Global Medical News

Physicians and hospitals now have the chance to test out bundled payments on a range of conditions under a new Medicare initiative.

In late August, officials at the Centers for Medicare and Medicaid Services released a request for applications (RFA) inviting physicians, hospitals, and other health care providers to participate in the Bundled Payments for Care Improvement initiative. The program, which was mandated under the Affordable Care Act, offers a variety of options for bundling payments for a hospital stay, for postdischarge services, or for both the hospital stay and the postdischarge care.

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Bundled pay is a major shift in how the government pays for medical care.

The move toward bundled payments is a major shift in how the government pays for medical care. Instead of paying hospitals, physicians, and other providers separately, this initiative would combine the payment over an episode of care for a specific condition. The aim of the program is to incentivize clinicians to work together and provide better continuity of care, resulting in better quality and lower costs.

"Today, Medicare pays for care the wrong way," Health and Human Services Secretary Kathleen Sebelius said during a teleconference to announce the bundling program. "Payments are based on the quantity of care, the amount of services delivered, not the quality of that care. And that leaves us too often with a system that actually can punish the providers that are most successful at getting and keeping their patients healthy."

The new bundling program offers four ways that health care providers can receive a bundled payment, three of which provide payment retrospectively and one that offers a prospective payment. For example, under some of the retrospective payment models, CMS and the providers would agree on a target payment amount for the episode of care and providers would be paid under the original Medicare fee-for-service system, but at a negotiated discount of 2%-3% or greater. At the end of the care episode, the total payment would be compared with the target price and providers would share in the savings, according to CMS.

The prospective payment model would work differently. Under that option, CMS would make a single bundled payment to the hospital to cover all services provided during the inpatient stay by the hospital, physicians, and other providers. That payment would offer at least a 3% discount to Medicare. Under this option, physicians and other providers would submit "no pay" claims to Medicare and the hospital would pay them out of the single bundled payment.

In addition to the options of prospective or retrospective payment, providers could choose how long the episode of care will be and what conditions they want to bundle payment for, and what services would be included in the payment. CMS officials said they wanted to make the program flexible so that a range of hospitals, physicians, and other providers could participate.

Although the application period has closed for organizations interested in Model 1, those interested in applying for Models 2, 3, and 4 have until Nov. 4 to do so. More information on the program is available at www.innovations.cms.gov/areas-of-focus/patient-care-models/bundled-payments-for-care-improvement.html.

Dr. Richard Gilfillan, the acting director of the CMS Innovation Center, which is overseeing the bundling initiative, said he expects that hundreds of organizations will apply. CMS will consider a number of factors in choosing participants for the program including the best proposals for care improvement, the number of patients involved, and the conditions addressed, and the price discounts offered, he said.

The program is a unique opportunity for hospitals to redesign their systems to promote better care coordination, Dr. Gilfillan said, and have that effort supported through Medicare payments.

The idea is to eliminate the traditional barriers between physicians and other providers – both inpatient and outpatient – all of whom may be involved in the care of a single condition, said Dr. Nancy Nielson, senior adviser to the CMS Innovation Center and past president of the American Medical Association. "I do believe that both physicians and hospitals will find this [to be] an opportunity that's flexible enough to give them the opportunity to begin to learn how to get paid for care differently," she said.

The AMA was still reviewing the bundled payment details at press time, but praised CMS for making the program flexible. Dr. Cecil B. Wilson, AMA immediate past president, said the organization will urge federal officials to encourage applications for physician-led bundling projects. "For this to be successful, and for physicians to participate actively, then they need to be a part of that process rather than just some larger corporation or larger hospital system or health plan that's organizing these," he said. "We think those are important as well, but we also think it's important that physicians be a part of that leadership."

While physicians working in large group practices have had some experience with bundled payments, most doctors aren't prepared for these types of changes, Dr. Wilson said. So the AMA is also recommending that CMS provide technical assistance to interested physicians. ■

CMS Eases Requirements for E-Prescribing

BY FRANCES CORREA
Elsevier Global Medical News

Based on feedback from physicians and health care providers, the final federal e-prescribing regulations are more flexible and contain more exemptions, the Centers for Medicare and Medicaid Services announced.

The changes come after concern that the program criteria should be more aligned with the Medicaid incentive program for electronic health records, according to CMS officials.

"[The changes] will encourage more doctors and other health care professionals to adopt this technology and give them the added flexibility to help them succeed," Dr. Patrick Conway, chief medical officer at CMS and director of the agency's Office of Clinical Standards and Quality, wrote in a blog post announcing the change. "With electronic prescribing, providers can better manage patient prescriptions, reducing drug interactions or other preventable prescription errors." Under the Medicare Electronic Prescribing Incentive Program, eligible prescribers who meet the e-prescribing criteria will get a 1% bonus payment for 2011 and 2012 and a 0.5% bonus in 2013. Those who do not meet the criteria in 2012 will be penalized 1% of Medicare payments; the penalty will escalate in 2013 and 2014.

Under the final rule, prescribers who use certified electronic health records can claim this as a "qualified" e-prescribing system. This move was designed to more closely align the e-prescribing program with the program that offers incentives for meaningful use of electronic health records, CMS officials said.

The final rule contains hardship exemptions for those who live in a rural area without high-speed Internet access and those who work where there are not enough pharmacies that can take electronic prescriptions. In addition, the final rule creates additional hardship exemption categories. Eligible professionals have to demonstrate that they have registered to participate in the Medicare or Medicaid EHR incentive program and have adopted certified EHR technology; an inability to electronically prescribe due to local, state, or federal law (this primarily applies to prescribing of narcotics); very limited prescribing activity; or insufficient opportunities to report the e-prescribing measure.

The deadline to apply for a hardship exemption has been extended until Nov. 1, 2011, according to CMS officials.

Even with the changes, however, some physicians still have concerns. The American Medical Association said it is worried about the amount of time physicians will have to apply for the exemptions.

"We remain concerned that physicians will be hit with a penalty and are not being given enough time to comply with the e-prescribing program criteria to avoid this penalty," said Dr. Cecil Wilson, AMA immediate past president. ■

COMMENTARY

Dr. Stuart Garay, FCCP, comments: A crucial addition to the final regulations is the broadening of the hardship exemption categories. However, unless you fall under one of the hardship exemption categories, you should e-prescribe. In addition, there will be another 6-month reporting period in which CMS will require at least 10 more e-prescriptions under the threat of another penalty. Doctors who fail in 2012 will incur a 1.5% Medicare cut in 2013. Don't leave money on the table!

Medicaid Spending Varies Widely

BY MARY ELLEN SCHNEIDER
Elsevier Global Medical News

A look at Washington state's Medicaid program could provide some clues for how to control costs as states prepare for the massive 2014 expansion of Medicaid under the Affordable Care Act.

Washington has been able to provide widespread access to outpatient services and prescription drugs, while keeping down spending on inpatient care, according to an analysis in Health Affairs (doi: 10.1377/hlthaff.2011.0106).

The per beneficiary cost for inpatient stays was about 35% below the national average in Washington state, while outpatient visits and prescriptions were each 15% above the national average, according to authors Todd P. Gilmer, Ph.D., and Richard G. Kronick, Ph.D., who were both at the University of California, San Diego, when the article was written. Dr. Kronick is now a deputy assistant secretary for health policy at the Department of Health and Human Services.

Dr. Gilmer and Dr. Kronick analyzed Medicaid claims data from 2001 to 2005 to see how the volume and the price of services affected the variation in spending across the states. They limited the analysis to claims for Medicaid-only, disabled beneficiaries receiving cash assistance.

"Several states are using their Medicaid resources in a way that's helping to reduce the need for more expensive hospital care," Dr. Gilmer said in a statement. "This suggests that there is a great deal of room for innovation in Medicaid. By increasing access to primary care and experimenting with team-based delivery models and low-cost providers, states may be able to improve quality while reducing Medicaid spending."

For example, the Medicaid programs in Connecticut, Massachusetts, New Hampshire, and Vermont spent more than most on prescription costs and outpatient visits, but had a lower-than-average number of hospital days. The inpatient and outpatient spending offset each other, the researchers wrote, resulting in average overall spending that was just below the mean among all states.

The researchers also found that having a large primary care workforce was associated with reduced hospital stays for some chronic conditions.

The authors received funding from the Robert Wood Johnson Foundation's Changes in Health Care Financing and Organization initiative. ■

Medicare Aims to Cut Paperwork

Physicians and their staffs may have a little less insurance paperwork to do, thanks to a new Medicare regulation.

The interim final rule, now published in the Federal Register, places two rules on electronic health care transactions: one to make it easier to determine patients' health care coverage and the other to ascertain the status of a submitted claim.

Currently, when a physician's office staff seeks information on patient health care coverage, they may have to make the request in a different format for each health plan, but under the operating rules set out by Medicare the format will be standardized across all health plans. The changes, mandated under the Affordable Care Act, will go into effect Jan. 1, 2013.

The new requirements are based largely on operating rules developed by the Council for Affordable and Quality Healthcare's Committee on Operating Rules for Information Exchange (CAQH CORE), an industry coalition that works on administrative simplification issues. The CAQH CORE rules are currently in use on a voluntary basis, Centers for Medicare and Medicaid Services officials said.

The CMS estimates that the adoption of these rules will save physicians and health plans about $12 billion over the next decade, largely because of fewer phone calls between physicians and health plans, reduced paperwork and postage costs, increased opportunities to automate the claims process, and fewer denials.

—Mary Ellen Schneider

Hospitalization Linked to Stoppage of Chronic Meds

BY MARY ANN MOON
Elsevier Global Medical News

Hospitalization raises the risk that patients' long-term medications for chronic diseases will be discontinued unintentionally, according to a report.

That risk is further heightened with ICU care, which suggests that the more patients are transitioned from site to site and from clinician to clinician, the greater the chance that their long-term medications (statins, antiplatelet or anticoagulant agents, levothyroxine, respiratory inhalers, and gastric acid-suppressing drugs) will get lost in the shuffle.

Discontinuing these necessary medications appears to raise patients' risk of death, further hospitalization, and ED visits for up to 1 year after discharge, said Dr. Chaim M. Bell of St. Michael's Hospital, Toronto, and his associates.

"These findings emphasize the importance of a systematic approach to transitions in health care to ensure medication continuity," they noted.

The investigators conducted a population-based cohort study of all hospitalizations of patients aged 66 years and older in Ontario between 1997 and 2009 to examine medication continuity. They reviewed the records of 396,036 patients who had been taking any of the five types of medications for chronic disease listed above for at least 1 year.

In all, 160,568 of these study subjects were hospitalized during the study period, including 16,474 who were admitted to the ICU; the remaining 208,468 who were not hospitalized served as control subjects. The rate of patients who failed to refill prescriptions of the five categories of medication within 90 days of discharge was calculated.

The study investigators excluded cases in which patients developed complications or contraindications to their medications, or otherwise had a clear reason for discontinuing a drug. They also controlled for confounding factors that could influence stopping a medication, such as comorbid disease burden and the number of physician contacts that occurred during the year preceding hospitalization.

MANY MEDICATIONS FOR CHRONIC DISEASES ARE PURPOSELY DISCONTINUED, BUT RESTARTING THEM IS FORGOTTEN OR OVERLOOKED.

Drugs in all five medication categories were significantly more likely to be discontinued after hospitalization than in the controls.

Rates of unintentional discontinuation were highest for antiplatelet/anticoagulants (19.4%), followed by statins (13.6%), gastric acid suppressors (12.9%), levothyroxine (12.3%), and respiratory inhalers (4.5%). The corresponding rates for control subjects were 11.8%, 10.7%, 9.4%, 11%, and 3%, respectively.

Rates of unintentional discontinuation were even higher among ICU patients in four of the five medication categories (22.8% for antiplatelet/anticoagulants, 15.4% for gastric acid suppressors, 15% for levothyroxine, and 14.6% for statins).

In a secondary analysis, the unintentional discontinuation of antiplatelet/anticoagulants and of statins was associated with higher risk of the combined outcome of death, further hospitalization, or emergency admission for up to 1 year after hospital discharge.

"This underscores the widespread prevalence of potential errors of omission and the risk for long-term harm following hospitalization," Dr. Bell and his colleagues said (JAMA 2011;306:840-7).

Although this study was not designed to assess how it is that necessary medications get "dropped" unintentionally, previous studies have suggested that miscommunication during transitions of care is not the only contributor. Many medications for chronic diseases are purposely discontinued during a critical illness, but restarting them is forgotten or overlooked after the acute event resolves.

Previous research also found that unintentional discontinuation of medications is common, but they were primarily single-site, cross-sectional studies. In contrast, "our study examined potential errors of omission on a systemwide basis for an extended period in a diverse patient population with a focus on long-term medications for chronic diseases," the investigators wrote.

COURTESY DR. CHAIM M. BELL

"This underscores the widespread prevalence of potential errors of omission," said Dr. Chaim M. Bell and coauthor Stacey Brener.

"Even though our study cohort only included elderly patients [aged 66 and older], the findings are likely generalizable to the general population," Dr. Bell and his coauthors concluded.

The study was funded by the Canadian Institutes of Health Research, the Institute for Clinical and Evaluative Sciences, and the Ontario Ministry of Health and Long-Term Care. ■

COMMENTARY

Dr. Jeana O'Brien, FCCP, comments: Dr. Bell and his colleagues have confirmed with data what has been anecdotally noted for some time – chronic medications are often discontinued in ICU and other hospitalized patients and not restarted. While this is appropriate in some situations (anticoagulants in patients presenting with gastrointestinal hemorrhage), this is often an oversight in the transition of care. With increased availability of medication information from electronic health records, scrutiny toward medication reconciliation, and nonpayment for readmissions, this issue will hopefully be remedied. Developing processes to consistently enforce reconciliation against home meds upon transfer from the ICU, and again at hospital discharge, will have lasting benefits for all patients. (See Critical Care Commentary, p. 18.)

Beware of Curtain! Pathogens Plentiful on Hospital Partitions

BY DOUG BRUNK
Elsevier Global Medical News

CHICAGO – If you think the privacy curtains at your health care facility are free of potentially harmful bacteria, think again.

Within 1 week of being laundered, 92% of hospital curtains were contaminated with pathogens that included methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) species, results from a single-center study showed.

"Usually when health care workers walk into a patient room, they'll wash their hands, grab the curtain, pull it aside, and then touch the patient, without realizing that they touched the curtain," Marin L. Schweizer, Ph.D., commented in an interview during a poster session at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy.

VITALS

Major Finding: Over a period of 3 weeks, 95% of all hospital privacy curtains demonstrated contamination with at least one potentially harmful bacterium. Vancomycin-resistant methicillin-resistant *S. aureus* or *Enterococcus* spp. were isolated from 42% and 21% of the curtains, respectively.

Data Source: A study of 180 swab cultures from 43 privacy curtains in 30 rooms at the University of Iowa Hospitals and Clinics.

Disclosures: The study was funded by PurThread, a manufacturer of antimicrobial fabrics for use in health care settings. One of the study investigators, Dr. Eli Perencheviche, is a paid consultant for PurThread. None of the curtains studied were made by PurThread.

"The message here is that health care workers should wash their hands after touching privacy curtains and before touching the patient."

Over a 3-week period, Dr. Schweizer and her associates obtained 180 swab cultures from 43 privacy curtains in 30 rooms at the University of Iowa Hospitals and Clinics (8 medical intensive care units, 7 surgical ICUs, and 15 medical wards). They obtained the cultures twice weekly from an 800-cm^2 area on the leading edge of each curtain, and marked each curtain to determine when it was changed.

Standard microbiologic methods, including broth enrichment, were used to determine contamination. To distinguish persistence of pathogens on curtains from recontamination, all MRSA and VRE were typed using pulsed-field gel electrophoresis.

Of the 13 curtains placed during the study, 12 (92%) showed contamination within 1 week, while 41 of the 45 curtains (95%) showed contamination on at least one occasion.

"We thought the prevalence would be high, but we didn't think it would be that high," commented Dr. Schweizer of the department of general internal medicine at the University of Iowa, Iowa City.

She went on to report that VRE and MRSA were isolated from 42% and 21% of the curtains, respectively. Eight curtains were contaminated with VRE at more than one time point: three with persistence of a single genetic type and five with genetic types over time. "This shows that there are lots of pathogens on the curtains," Dr. Schweizer said. "They stick around for a long time and they're constantly being recontaminated."

Two-thirds of all swab cultures (66%) were positive for either *S. aureus*, *Enterococcus* spp. (44%), or gram-negative rods (22%). ■

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Please send a cover letter and curriculum vitae to the attention of David Norton, M.D., MICU Director, 231 Albert Sabin Way, MSB 6053, Cincinnati, OH 45267-0564, or email **david.norton@uc.edu**

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Chief, Division of Pulmonary Critical Care and Sleep Medicine

North Shore-Long Island Jewish Health System (NSLIJHS) and **Hofstra University School of Medicine** are conducting a national search for a **Chief, Division of Pulmonary Critical Care and Sleep Medicine** for North Shore University Hospital (NSUH) and Long Island Jewish Medical Center (LIJMC).

This position is an opportunity for a highly distinguished physician to provide leadership and direction for the Division of Pulmonary Critical Care and Sleep Medicine at NSUH and LIJMC in addition to developing the Division at the new medical school. The ideal candidate will have national and/or international recognition as well as experience working in an academic medical center or health system. The candidate must have a strong clinical orientation, be familiar with medical school curricular needs, the conduct of translational and clinical research, and have the capability to manage the financial/business affairs of a complex multi-site department. Candidates for this position must be board-certified and eligible for a NY State medical license.

North Shore-LIJ Health System provides compassionate, high-quality healthcare in the greater Long Island region through its 16 hospitals and more than 38, 000 employees. NSLIJHS is the 3rd largest, non-profit, secular healthcare system in the U.S. and the 9th largest employer in the New York City metropolitan area.

The Chief's primary role at the Hofstra University School of Medicine will be to build and grow a top-tier academic Division of Pulmonary Critical Care and Sleep Medicine, including building a strong collaborative effort with the Feinstein Institute of Research, and be responsible for all educational activities, including the development of a comprehensive curriculum, oversight of medical student training, and recruitment of faculty. At the Health System, the Chief will have direct responsibility for medical services at NSUH and LIJMC. The incoming Chief will oversee the combined faculty members, voluntary physicians and fellows across both campuses.

Interested individuals should submit a letter or email expressing interest with a curriculum vitae to:

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