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Glucocorticoid-related growth impairment has a lasting effect on potential adult height, study findings suggest.

Budesonide for Kids Reduces Adult Height

BY MICHELE G. SULLIVAN
IMNG Medical News

Long-term use of inhaled budesonide is associated not only with slowed growth in prepubertal children, but with reduced final adult height as well.

An 8-year observational study found that children who had used budesonide during an asthma treatment trial were more than 1 cm shorter than those who used nedocromil or placebo. The findings suggest that glucocorticoid-related growth impairment has a lasting effect on potential adult height, H. William Kelly, Pharm.D., and his colleagues wrote in the the New England Journal of Medicine (N. Engl. J. Med. 2012;367:904-12 [doi: 10.1056/NEJMoa1203229]).

The prospective study followed 943 children who had participated in the Childhood Asthma Management Program (CAMP) trial. CAMP randomized children with asthma aged 5-13 years to placebo, 400 mcg/day budesonide, or 16 mg/day nedocromil.

Initial follow-up averaged 4.3 years, with height measured once or twice a year for the subsequent 8 years. Final height was measured at a mean age of 25 years.

The mean adult height in the budesonide group was 171.1 cm – significantly shorter than the 172.3 cm in the placebo group. Mean adult height in the nedocromil group was almost the same as in the placebo group (172.1 cm).

Women in the budesonide group were particularly affected; they were a mean of 1.8 cm shorter than women in the placebo group. Men who took

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Beta-Blockers: Too Little in COPD, Too Soon in MI

Bronchospasm concerns may be ebbing.

BY BRUCE JANCIN
IMNG Medical News

ESTES PARK, COLO. – Beta-blockers may be underprescribed in the setting of chronic obstructive pulmonary disease, yet overused in the early treatment of acute myocardial infarction, recent surprising evidence suggests.

Cardiovascular disease and COPD are closely intertwined through the effects of smoking. Yet the notion of prescribing beta-blockers in patients with COPD challenges the conventional wisdom. Most physicians avoid the practice, even in patients with concomitant cardiovascular disease, because of worries about triggering bronchospasm and perhaps blocking the bronchodilating benefits of beta-agonist inhaler therapy.

But data from a Scottish retrospective cohort study strongly suggest these concerns are misplaced, asserted Dr. Mel L. Anderson, chief of the hospital medicine section and associate chief of the medical service at the Denver VA Medical Center. He spoke at a conference on Internal Medicine sponsored by the University of Colorado

The NHS Tayside Respiratory Disease Information System (TARDIS) is a disease-specific database developed 11 years ago to help Scottish primary care physicians and pulmonologists manage patients with COPD. The TAYSIDE investigators recently reported on 5,977 patients above age 50 with confirmed COPD who were followed for a mean of 4.4 years. The study population included 819 patients on beta-blockers, nearly 90% of

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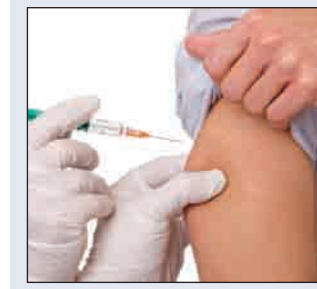
INSIDE



Tiotropium Cut Asthma Exacerbations

BY MARY ANN MOON
IMNG Medical News

Adding tiotropium to standard combination therapy may help reduce exacerbations in some adults whose asthma is poorly controlled despite the use of inhaled glucocorticoids and long-acting beta-agonists, according to two randomized, controlled trials published in the New England Journal of Medicine.

However, tiotropium use did not increase the number of symptom-free days or boost patients' asthma-related quality of life scores.

Compared with placebo, tiotropium administered once daily via a soft-mist inhaler significantly lengthened the time to a severe exacerbation of asthma, reduced the number of exacerbations, and provided "modest" bronchodilation when added to inhaled glucocorticoids and LABAs, said Dr. Huib A.M. Kerstjens of the University of Groningen (the Netherlands) and the Groningen Research Institute for Asthma and COPD, and his

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Beta-Blockers May Be COPD Tool

Therapy • *from page 1*

which were relatively cardioselective agents such as bisoprolol or atenolol.

In a matched propensity score analysis, patients on a beta-blocker plus various combinations of respiratory medications had a 22% decreased risk of all-cause mortality and a 50% reduction in the risk of hospitalizations for COPD during the follow-up period.

THE STUDY SHOULD AT LEAST MAKE YOU FEEL COMFORTABLE THAT IT'S SAFE TO OFFER BETA-BLOCKER THERAPY TO COPD PATIENTS, PROVIDED THEY DON'T HAVE ASTHMA.

The mortality benefit associated with beta-blocker therapy proved independent of the presence or absence of overt cardiovascular disease, as similar reductions were seen in deaths as a result of COPD and myocardial infarction (BMJ 2011;342:d2549]).

"Yes, this is an observational study and so you have to worry about selection bias, but if anything, it should at least make you feel comfortable that it's safe to offer beta-blocker therapy to COPD patients, provided you're sure they don't have asthma," Dr. Anderson remarked.

He also highlighted another emerging issue with regard to beta-blockers, this one involving their widespread inappropriate use in the early treatment of MI in patients with one or more risk factors for cardiogenic shock.

Investigators utilized the American College of Cardiology registry known as ACTION Registry-GWTG to study outcomes in 34,661 patients with ST elevation MI (STEMI) and non–ST-segment MI (non-STEMI) who received beta-blocker therapy within the first 24 hours after MI presentation at 291 participating U.S. hospitals. The registry is part of the American College of Cardiology's National Cardiovascular Data Registry.

The relevant ACC/American Heart Association Guidelines for Unstable Angina/Non-STEMI (J. Am. Coll. Cardiol. 2007;50:e1-e157) and STEMI (J. Am. Coll. Cardiol. 2008;51:210-47) recommend caution in giving beta-blockers in the first 24 hours in patients with risk factors for cardiogenic shock.

Yet in the ACTION Registry-GWTG study, 45% of the STEMI patients treated with early beta-blockers and 63% of early beta-blocker recipients with non-STEMI had one or more cardiogenic shock risk factors identified in the guidelines on the basis of findings in the earlier COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) study (Lancet 2005; 366:1,622-32).

Moreover, the ACTION Registry data demonstrated that early beta-blocker therapy in patients with risk factors for cardiogenic shock was associated with significantly worse outcomes. For example, the combined rate of in-hospital cardiogenic shock or death was 1.3% in beta-blocker recipients with no shock risk factors, 4.8% in those with one of the risk factors, and 8.1% in those with two or more (Am. Heart J. 2011;161:864-70).

The cardiogenic shock risk factors that grew out of the COMMIT study are age greater than 70 years, systolic blood pressure below 120 mm Hg at presentation, a heart rate in excess of 110 bpm, and 12 hours or longer since symptom onset in STEMI patients.

"I bring this to your attention because these risk factors are not going to jump out at you. They fit a lot of the patients we see, but statistically they have an excess risk for cardiogenic shock, and you should either not use beta-blockers early or be incredibly careful in doing so in those patients," Dr. Anderson advised.

Asked by a concerned audience member how physicians who decline to prescribe a beta-blocker for patients with acute coronary syndrome and one or more shock risk factors can avoid taking a hit for noncompliance with a Joint Commission and Medicare core performance indicator, the hospitalist replied that the key is to avoid "early" use of the medication in patients with cardiogenic shock risk factors.

Once 24 hours have gone by and the patient has been stabilized and has better blood flow to the heart, prescribing a beta-blocker may well be appropriate, he said.

Dr. Anderson reported having no financial conflicts. ■

COMMENTARY

Dr. Vera DePalo, FCCP, comments: With quality efforts focused on reducing hospitalizations and improving outcome in patients with COPD, it seems a new tool has been identified to help clinicians achieve these goals.

The NHS Tayside Respiratory Disease Information System database has revealed a significant decrease in all-cause mortality and a reduction by 50% in COPD hospitalizations for patients taking relatively cardio-selective beta- blockers and a combination of respiratory medications.

Cautious decision-making is advised in the initiation of beta-blockers in selected COPD patients and in giving beta-blockers during the first 24 hours following myocardial infarction to patients with risk factors for cardiogenic shock.

IN THIS ISSUE

Dr. W. Michael Alberts, FCCP, is Medical Editor in Chief of CHEST PHYSICIAN.

CHEST PHYSICIAN

IMNG MEDICAL MEDIA

CHEST PHYSICIAN, the newspaper of the American College of Chest Physicians, provides cutting-edge reports from clinical meetings, FDA coverage, clinical trial results, expert commentary, and reporting on the business and politics of chest medicine. Each issue also provides material exclusive to the members of the American College of Chest Physicians. Content for **CHEST PHYSICIAN** is provided by International Medical News Group, A Frontline Medical Communications company. Content for NEWS FROM THE COLLEGE is provided by the American College of Chest Physicians.

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cIAI

Complicated skin and skin structure infections caused by *Escherichia coli*, *Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus agalactiae*, *Streptococcus anginosus* grp. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Streptococcus pyogenes*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, and *Bacteroides fragilis*

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

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- To reduce the development of drug-resistant bacteria and maintain the effectiveness of TYGACIL and other antibacterial drugs, TYGACIL should be used only to treat infections proven or strongly suspected to be caused by susceptible bacteria. As with other antibacterial drugs, use of TYGACIL may result in overgrowth of nonsusceptible organisms, including fungi
- The most common adverse reactions (incidence >5%) are nausea, vomiting, diarrhea, infection, headache, and abdominal pain
- Prothrombin time or other suitable anticoagulant test should be monitored if TYGACIL is administered with warfarin
- Concurrent use of antibacterial drugs with oral contraceptives may render oral contraceptives less effective
- The safety and effectiveness of TYGACIL in patients below age 18 and lactating women have not been established

Please see brief summary on adjacent page.

REFERENCE: 1. TYGACIL® [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals Inc; 2011.

Tygacil® tigecycline IV

H5N1 Called an Entrenched Threat to Human Health

BY DOUG BRUNK
IMNG Medical News

SAN FRANCISCO – The pathogenic avian influenza A(H5N1) virus remains entrenched in poultry in many countries and is unlikely to be eradicated, according to Dr. Malik Peiris.

"Over the past 15 years the virus has spread through Asia and to part of Africa. Even this year there have been poultry outbreaks in about nine countries, especially in Egypt but also in Asia and Indonesia," said Dr. Peiris, director of the Center of Influenza Research at the University of Hong Kong. "That, I think, is the real cause for concern."

He spoke at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy.

So far, human disease has been uncommon, but the potential for human exposure to H5N1 is massive, he said. The reasons for viral spread are multifactorial, including the prevalence of backyard flocks of poultry and game birds, which are extremely common in parts of Asia, and the fact that the virus can infect ducks. "These ducks are moved from paddy field to paddy field," he said. "They graze on fallen rice in these paddy fields, and they move the virus without any ill effect to themselves. Live poultry markets are also a reservoir and amplifier. Some lineages of this virus can be moved long distances through migration of wild birds, but it is not clear whether wild birds are a true reservoir of this virus."

To date, Dr. Peiris said, 608 human cases of H5N1 infection have been reported from 15 countries in Asia and Africa. Of these, 359 (59%) have been fatal. The incubation period is 2-3 days, and the virus presents as severe viral pneumonia. "It's rapidly progressing in previously healthy younger persons," he said. "It's not the type of pneumonia [caused by] complications of influenza that you see with typical seasonal flu, which is at the extremes of age and is often associated with secondary bacterial superinfection. These are perfectly healthy people."

Virus clades from Indonesia seem to carry the greatest severity, Dr. Peiris said, followed by clades from the Middle East and those from other parts of Asia. There appears to be lower mortality among affected children under age 5 and among patients who receive oseltamivir treatment within 2 days of symptom onset.

The virus rapidly progresses in previously healthy younger persons, unlike seasonal flu.

DR. PEIRIS

"The virus strains are generally sensitive to oseltamivir, though different clades have a different range of sensitivity," Dr. Peiris said at the conference. "There are cases where antiviral resistance has been detected, with adverse outcomes."

According to World Health Organization guidelines published in 2007, "modified regimens of oseltamivir treatment, including twofold higher dosage, longer duration, and, possibly, combination therapy with amantadine or rimantadine (in countries where A[H5N1] viruses are likely to be susceptible to amantadines), may be considered on a case by case basis, especially in patients with pneumonia or progressive disease."

According to Dr. Peiris, data on this approach "are limited, but observational data suggest that a higher dose of oseltamivir is not associated with lower mortality."

While some experts argue that H5N1 viruses are inherently unable to transmit from human to human, two recent studies of ferrets suggest that airborne transmission is possible (Science 2012;336:1534-41 and Nature 2012;486:420-8). "While combinations of mutations are required for acquisition of mammalian transmissibility, some of these are individually present in some field isolates of H5N1 viruses, highlighting the need for enhanced and continued vigilance," Dr. Peiris noted.

The conference was sponsored by the American Society for Microbiology. Dr. Peiris is a scientific adviser for Crucell and is a consultant for GlaxoSmithKline. ■

Ten States Dealing With H3N2 Outbreak

BY DOUG BRUNK
IMNG Medical News

SAN FRANCISCO – The H3N2 virus could sicken 500-900 people in the United States by the end of 2012, surveillance studies by the Centers for Disease Control and Prevention suggest.

"Cooler weather is approaching, and it is likely that additional cases of H3N2v will be identified in the coming weeks," said Lyn Finelli, Dr.PH., chief of surveillance and outbreak response in the influenza division at the CDC's National Center for Immunization and Respiratory Diseases, Atlanta.

Between December 2005 and June 2012, there have been 36 human cases of swine influenza A virus infection identified, Dr. Finelli said at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy. "Identification has increased since 2009" as novel influenza A became a reportable disease in 2007, better diagnostics became available at state health departments, and there has been greater awareness due to the 2009 pandemic H1N1 virus.

In 2011, public health officials in the United States identified 12 cases of H3N2v with the pandemic M gene from the 2009 pandemic H1N1 virus. Six were associated with exposure at agricultural

Antiviral treatment with oral oseltamivir or inhaled zanamivir is encouraged as soon as possible.

DR. FINELLI

fairs or farms and six were cases of human to human transmission.

This subtype continues to spike in prevalence. Between July 1 and Sept. 10, 2012, 302 cases of H3N2v infection with the M gene have been confirmed in the United States. The M gene "was thought to contribute to increased transmissibility of the pandemic H1N1 virus," Dr. Finelli noted. "In two animal studies it was shown to increase transmissibility for pandemic H1N1. … Various serologic studies to date suggest that children under 12 have very little protection against this virus."

An outbreak of H3N2v is occurring in 10 states, and 16 patients have been hospitalized. Indiana has the most confirmed cases, followed by Ohio and Wisconsin. "Ohio also has a large number of probable cases, many of whom are rapid test positive but who have not been tested with PCR, so that state probably has more cases than Indiana at this point," Dr. Finelli said.

The mean age of the 302 cases is 8 years, with a range between 4 months and 74 years, and the incubation period is 2-3 days. "The secondary attack rate is low," she said. "We only have 10 probable cases of human to human transmission. The duration of illness is 3-4 days and the period of infectiousness is unknown. We don't have enough secondary transmission to tell."

Of the 16 patients who have been hospitalized with H3N2v, 14 (87%) were 0-17 years of age and the remaining 2 were at least 18 years of age. The most common underlying condition is being 5 years of age or younger (38%), followed by asthma (19%), cancer or immune suppression (19%), and neurological disorder (13%). One patient died (7%).

Dr. Finelli and her associates have exposure data on 203 cases. Of these, 198 (98%) had either direct or indirect swine contact, or attended a state or county fair.

Antiviral treatment with oral oseltamivir or inhaled zanamivir is encouraged as soon as possible for patients with suspected H3N2v virus infection, especially hospitalized patients or patients with severe or progressive illness, she said. "All non–high-risk outpatients without underlying medical conditions can be started within 48 hours of illness onset."

"Surveillance guidance for state and local public health has focused on increasing collection of PCR quality specimens from patients presenting with influenza-like illness in high risk groups," Dr. Finelli said.

Two candidate H3N2v vaccines have been identified and clinical trials are now under way, she said. The conference was sponsored by the American Society for Microbiology. Dr. Finelli reported having relevant financial disclosures. ■

IDSA Updates Flu Readiness Principles

BY ELIZABETH MECHCATIE
IMNG Medical News

Seasonal influenza vaccination should be required for all health care workers, according to updated seasonal and pandemic influenza principles from the Infectious Diseases Society of America.

Incorporating lessons learned during the 2009-2010 H1N1 influenza pandemic and warning against complacency about the inevitability of another pandemic, the revised IDSA principles debuted in a document titled "Pandemic and Seasonal Influenza Principles for United States Action" (idsociety.org/influenzaprinciples/)

The society revamped its flu guidance to help Department of Health and Human Services (HHS) officials establish priorities as they implement the Pandemic and All-Hazards Preparedness Act, which is being reauthorized by Congress.

IDSA last released such flu preparation and response principles in January 2007, before the 2009 H1N1 influenza pandemic. The emergence of the novel influenza H1N1 strain showed that, "in addition to severe illness and death, the spread of new influenza strains can cause significant societal and economic disruption and anxiety, and, in extreme cases, may threaten economic and national security."

The document outlines 10 principles, including strengthening influenza vaccination efforts and developing strategies to communicate with the public and medical professionals during a pandemic. It also advocates improved influenza surveillance and coordination between HHS and other federal and global partners, and well as boosting the accuracy and availability of diagnostic tools.

In addition, IDSA calls for enhanced availability of current antiviral drugs, as well as the development of new, simple-to-use antiviral drugs. The document highlights the need for antibacterial drugs to treat secondary infections.

IDSA also addresses the need to protect health care workers during seasonal and pandemic influenza outbreaks, and it recommends that annual seasonal influenza vaccination be required for all health care workers "through rules, regulations, policies, or laws."

During a pandemic, health care workers directly taking care of patients should be in the group with highest vaccination priority. And long-term prophylaxis with antivirals can be considered "when medically appropriate and as supplies permit." ■

COMMENTARY

Dr. Marcos I. Restrepo, FCCP, comments:

We should commit to all-strategies to diagnose, prevent, and treat flu in our communities and patients. It should be a priority before new pandemias will arrive. Organizations, institutions and health care providers should be proactive rather than reactive to approach this well known and ongoing problem. It is important to address, evaluate, and implement these preparedness principles, and continuous updates are not only important but necessary.

'Ethical' Duty Calls for Vax

BY HEIDI SPLETE
IMNG Medical News

WASHINGTON – Approximately 42% of the U.S. population and 67% of health care workers received influenza vaccinations last year, according to data from the Centers for Disease Control and Prevention.

"I believe that the immunization of the health care provider community is both an ethical and professional responsibility," said Dr. William Schaffner, past president of the National Foundation for Infectious Diseases which sponsored a press conference.

"It is for two reasons: The first and most important is a patient safety issue, so we do not transmit our influenza infection to our patients.

"The other reason is, when influenza strikes, we need to be vertical, not horizontal," he continued. "We need to be ready to provide health care during that period of great community stress," said Dr. Schaffner, chair of preventive medicine at Vanderbilt University, Nashville, Tenn.

This year's vaccine contains a new A virus and a new B virus, according to the CDC. ■

Progress Seen in Cutting Pneumococcal Infections

BY BRUCE JANCIN
IMNG Medical News

VAIL, COLO. – American medicine emphatically surpassed the Healthy People 2010 goal for reduction of invasive *Streptococcus pneumoniae* infections well ahead of schedule in both of the highest-risk target groups: children under age 5 years and seniors. And tougher 2020 objectives are already well within striking distance.

"We get an A+ on this," Dr. Mary P. Glodé commented at the annual pediatric infectious diseases conference sponsored by Children's Hospital Colorado.

The Healthy People 2010 objective was to reduce the incidence of invasive *S. pneumoniae* infections to 46 cases per 100,000 among children under age 5 years and to 42 per 100,000 persons age 65 or older. The actual 2010 rates were 19 and 36 per 100,000, respectively.

Between 1999 and 2010, the annual rate of invasive pneumococcal disease in children under 5 plummeted by 86% as a result of the 2000 licensure of the pneumococcal conjugate vaccine 7 (PCV 7) .

The rate also fell by 50% during that period among seniors, even though they didn't receive the vaccine. This is ascribed to herd immunity said Dr. Glodé, head of the section of pediatric infectious disease at the University of Colorado, Denver, and Children's Hospital Colorado.

The Healthy People 2020 goal is to reduce invasive pneumococcal infections in children under age 5 to 12 per 100,000, and in seniors to 31 per 100,000.

The expectation is that the target in children will be met, as a consequence of the Spring 2010 recommendation Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (ACIP) that all children aged 2-59 months be vaccinated with PCV 13, which contains the PCV 7 serotypes plus six others causing invasive disease.

The hard unanswered question concerns the best way to get the nation's seniors to the 2020 target. The rate of invasive pneumococcal disease is higher in persons aged 65 and older than in any other age group, as is associated mortality.

Late last year, the Food and Drug Administration licensed PCV 13 for use in people aged 50 and up. But that does not necessarily mean it will see widespread use. There has been no official recommendation from the ACIP that the vaccine be routinely used in this population.

ACIP also noted that one-quarter of all cases of invasive pneumococcal disease in seniors are caused by 11 serotypes in the PPSV 23 vaccine that are not included in the PCV 13 vaccine, which further complicates the situation. PPSV 23 has been approved since 1983 and is recommended for use in all adults over age 65 and in younger adults with certain medical conditions, including chronic lung disease.

Dr. Glodé served on the data safety monitoring board for trials of an unrelated Pfizer vaccine. ■

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Early NSCLC Patients Living Longer After Radiotherapy

Good news for sickest patients, but 'at least 16%' still don't get necessary care, investigator says.

BY MIRIAM E. TUCKER
IMNG Medical News

Median overall survival increased significantly among patients with stage I non–small cell lung cancer over the last decade – in particular, those treated with radiation therapy alone, according to an analysis of the Surveillance, Epidemiology, and End Results database.

The median survival for all treatment groups increased by 27%, from 44 months during 1999-2003 to 56 months during 2004-2008. For those treated with radiation alone – who would likely be the sickest patients since they would not have been considered candidates for surgery – median overall survival improved by 31%, from 16 to 21 months. Both changes were statistically significant (log rank *P* less than .0001).

"Stage I NSCLC [non–small cell lung cancer] patients who receive radiation therapy alone are surviving longer than they used to," Dr. Nirav S. Kapadia said in a press briefing from the Chicago Multidisciplinary Symposium in Thoracic Oncology.

A change in the survival of patients treated with surgery could not be detected, as median survival has not yet been reached, he and his coauthors reported.

Until recently, surgery has been the primary treatment for stage I NSCLC. However, as recent advances in radiotherapy (RT) such as stereotactic body radiation therapy have allowed dose escalation with more precise tumor targeting, the use of RT has increased, and outcomes appear to have improved over time, said Dr. Kapadia, a chief resident in the department of radiation oncology at the University of Michigan, Ann Arbor.

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database encompasses about 25% of the U.S. population. This study compared SEER data on 27,469 patients with NSCLC treated during 1999-2003 with data from 26,195 patients treated during 2004-2008.

During 1999-2003, 64% of patients were treated with primary surgery, 14% received RT alone, 20% had neither treatment, and 2% had unknown treatment. In the later era, 70% of patients underwent primary surgery, 13% received primary RT, 16% had neither surgery nor RT, and 1% had unknown treatment.

The proportion receiving surgery alone increased from 60% to 67% during the two time periods. Thus, the rates of surgery increased from the earlier to the later period, but there was no significant difference in the number of patients who received radiotherapy, either as an adjunct to surgery or as definitive therapy, noted Dr. Kapadia.

He expressed concern about the significant proportion of patients – 20% in the earlier period and 16% in the later – who did not receive surgery or radiation. "At least 16% of patients are still not getting the care that they need – care that could save their lives. We must identify the barriers to treatment so that every patient has hope for a cancer cure," he said in a statement.

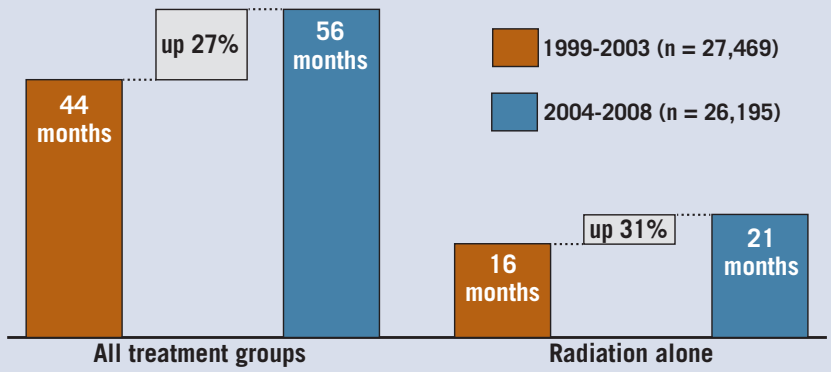
For the entire study period, factors significantly associated with higher risk of death after primary RT or surgery included age, African American race, large cell or squamous histology, and being unmarried. Significant protective factors included female sex and race listed as "other."

Dr. Kapadia noted that RT is advantageous in that it is noninvasive and is done on an outpatient basis. Moreover, local control rates with radiotherapy among patients who are too sick to undergo surgery are now approaching those of surgery.

Ongoing "coin flip" studies are currently comparing outcomes of radiation versus surgery in patients who would otherwise be fit for surgery. "Those are going to be very exciting studies. … But for right now I would say surgery is still the preferred modality, with a large body of evidence to support that statement," he said.

The symposium was sponsored by the American Society of Clinical Oncology, the American Society for Radiation Oncology, the International Association for the Study of Lung Cancer, and the University of Chicago. Dr. Kapadia and his coauthors had no financial disclosures. ■

Median Survival in Stage I Non–Small Cell Lung Cancer



Note: Based on analysis of patients from the SEER database.
Source: Dr. Kapadia

IMNG Medical Media

COMMENTARY

Dr. Jeana O'Brien, FCCP, comments: This report of improved median survival rates for patients with NSCLC treated with radiation alone is encouraging given the limited treatment options for these patients. Use of newer techniques such as stereotactic body radiation therapy allowing dose escalation and more precise tumor targeting may account for the improvement. Although the improved survival is modest, this suggests there may be additional patients with inoperable NSCLC who could be considered for radiation treatment.

Prophylactic Cranial Irradiation: No NSCLC Survival Boost

BY MIRIAM E. TUCKER
IMNG Medical News

Prophylactic cranial irradiation reduced the 5-year rate of brain metastases, but did not improve overall survival in a randomized trial that evaluated 340 patients without disease progression following potentially curative treatment for locally advanced non–small cell lung cancer.

The findings provide important confirmatory information regarding the effectiveness of prophylactic cranial irradiation (PCI) in decreasing the rate of brain failures, Dr. Elizabeth Gore said in a press briefing from the Chicago Multidisciplinary Symposium in Thoracic Oncology.

The trial closed early because of slow patient accrual, however, and did not enroll enough patients to answer the primary question: whether PCI improves overall survival in patients with stage III NSCLC.

"I'd like to emphasize the need for participation in clinical trials. This is particularly important in lung cancer, which is understudied" despite its being the leading cause of cancer death in the United States, said Dr. Gore, professor of radiation oncology at the Medical College of Wisconsin, Milwaukee.

Over a median follow-up of 24.2 months for all patients and 58.6 months for living patients, the 5-year rates of brain metastases were 17.3% for those randomized to receive PCI delivered to 30 Gy in 15 fractions, compared with 26.8% for patients randomized to observation. That difference was statistically significant ($P = .009$).

However, there were no significant differences in the 5-year rates of survival, (26.1% for PCI and 24.6% for observation), or disease-free survival (18.5% and 14.9%, respectively).

Of the patients with treatment failures, 10% of those receiving PCI and 23% in the observation group experienced failure in the brain initially. Brain metastases (BM) were the only component of first failure in 9.1% and 21.5% of patients with and without PCI, respectively.

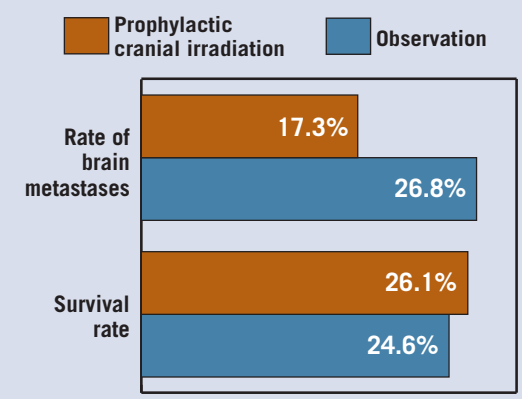
On multivariate analysis, PCI was significantly associated with decreased BM, whereas nonsquamous histology was associated with an increased risk of BM. The overall rate of BM in this trial was insufficient for reliable subset analyses by histology, Dr. Gore noted.

"Brain metastasis has a profound impact on patients with lung cancer in terms of quality of life. We need more information to determine which patients are most likely to derive a survival benefit from prophylactic cranial irradiation before this can become a part of standard management," she said.

The Chicago Multidisciplinary Symposium in Thoracic Oncology is sponsored by the American Society of Clinical Oncology, the American Society for Radiation Oncology, the International Association for the Study of Lung Cancer, and the University of Chicago.

Dr. Gore and her associates reported no financial disclosures. ■

5-Year Outcomes in NSCLC Patients



Note: Based on data for 340 patients without disease progresssion.
Source: Dr. Gore

IMNG Medical Media

Pages 8a—8b

Resistance to Second-Line TB Drugs Rises

BY MICHELE G. SULLIVAN
IMNG Medical News

Nearly 44% of multidrug-resistant tuberculosis cases tested in eight countries were also resistant to at least one second-line tuberculosis drug, according to results of an international prospective cohort study.

Extensively drug-resistant (XDR) strains were unexpectedly prevalent as well, particularly in South Korea and Russia, reported Tracy Dalton, Ph.D., of the Centers for Disease Control and Prevention, Atlanta, and colleagues. The report was published in The Lancet. These XDR isolates were detected in 6.7% of patients overall, with prevalence in South Korea (15%) and Russia (11%) exceeding the current World Health Organization global estimate (9.4%). The risk of XDR disease was four times greater in previously treated patients, and previous treatment with second-line drugs was consistently the strongest risk factor for resistance to these drugs (Lancet 2012 Aug. 30 [http://dx.doi.org/10.1016/S0140-6736(12)60734-X]).

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Multidrug-resistant tuberculosis is resistant to at least rifampicin and isoniazid, and accounts for 3·6%-4·8% of new tuberculosis cases worldwide.

Multidrug-resistant (MDR) tuberculosis is resistant to at least rifampicin and isoniazid, and accounts for 3·6%-4·8% of new tuberculosis cases worldwide. XDR tuberculosis is resistant to at least rifampicin, isoniazid, and one or more of the second-line antituberculosis drugs. XDR tuberculosis has been reported in 77 countries.

While the numbers varied between nations, investigators with the international Preserving Effective TB Treatment Study (PETTS) saw a concerning pattern: The prevalence of drug-resistant strains correlated with the time that the second-line drugs had become available through the Green Light Committee, a World Health Organization program designed to increase access to second-line antituberculosis agents.

"[Second-line drugs] had been available for 10 years or less in Thailand (7 years), the Philippines (9 years), and Peru (10 years), and these countries had the lowest rates of resistance," wrote Dr. Dalton of the Centers for Disease Control and Prevention. "By contrast, South Korea and Russia had the longest histories of availability (more than 20 years) and the highest rates of resistance."

PETTS was launched in 2003 to determine the risk factors for and frequency of acquired resistance to second-line therapies in people with MDR tuberculosis. In 2005, in light of burgeoning numbers, the program was modified to include data on people with XDR tuberculosis.

The current report focused on eight countries: Estonia, Latvia, Peru, the Philippines, Russia, South Africa, South Korea, and Thailand. Samples from patients with MDR tuberculosis were obtained from large clinical centers in each country during 2005-2008. Inclusion criteria were at least 30 days of treatment with a second-line antituberculosis drug, with sputum collection within 30 days before or after the initiation of therapy.

Of 1,540 isolates tested, 1,278 (83%) were MDR. Most of those patients (94%) had a history of tuberculosis, and of those, 71% had experienced it at least once before the tested case.

Of the entire group, 93% had received first-line therapy, but only 15% had received second-line drugs. South Africa had the lowest rate of second-line treatment (3%), while South Korea had the highest (54%).

The overall prevalence of resistance to any second-line drug was 43.7%, but the rate varied among the countries, from 33% in Thailand to 62% in Latvia.

Overall, 20% of isolates were resistant to at least one second-line injectable drug, ranging from 2% in the Philippines to 47% in Latvia. The Philippines also had the lowest prevalence of resistance to all injectables (0.3%), while South Africa had the highest (26%).

The overall resistance rate to at least one second-line oral drug was 27%. Resistance to at least one oral drug ranged from 13% in Estonia to 38% in Latvia; however, other countries also had a high prevalence, including South Korea (36%), the Philippines (32%), Russia (26%), and South Africa (22%).

A total of 6.7% of the isolates were XDR, with the highest prevalence in South Korea (15%) and the lowest in the Philippines (0.8%).

Prior treatment for MDR strains with the second-line drugs was the strongest risk factor for XDR tuberculosis, with a relative risk of 4.75 for injectables and 4 for oral medications.

Although countries with Green Light projects did have more cases, the risks ratios for different resistance types did not reflect the actual numbers, the authors noted.

Resistance to fluoroquinolones and second-line injectable drugs – but not to other oral second-line drugs – was significantly less prevalent in countries that had Green Light Committee-approved projects. "This difference was due to the very low prevalence of resistance to second-line drugs in the Philippines, which had the largest Green Light Committee project," the authors said.

The individualized numbers should be useful to national disease management efforts, the researchers added. "Our country-specific results can be extrapolated to guide in-country policy for laboratory capacity and for designing effective treatment recommendations."

PETTS data collection continues, they noted. "The effect of the Green Light Committee initiative in combating acquired resistance to second-line drugs, the timing of acquired resistance, and the role of specific genetic mutations in different regions of the world are also being assessed."

The U.S. Agency for International Development, the Centers for Disease Control and Prevention, the National Institutes of Health, and the Korean Ministry of Health and Welfare sponsored the study. The authors declared no financial conflicts. ■

In Obese, Linezolid Tops Vancomycin for MRSA Pneumonia

BY M. ALEXANDER OTTO
IMNG Medical News

SAN FRANCISCO – Linezolid works better than vancomycin in obese patients with MRSA pneumonia, according to an industry-supported analysis.

Clinical success – ICU or hospital discharge by day 14 in the absence of death, therapy change, or intubation – was more likely among 49 patients with body mass indices of 30 or more treated with 600 mg of linezolid IV or orally every 12 hours, the standard dose, than among 740 treated with standard dosing of vancomycin (HR 1.77, 95% CI 1.18-2.64). The findings come from a national retrospective cohort analysis of Veterans Affairs hospital data. The study was funded in part by Pfizer, which markets linezolid as Zyvox.

"Clinical success rates were higher [in obese patients] with linezolid. We don't know exactly why," lead investigator Aisling Caffrey, Ph.D., assistant professor of pharmacoepidemiology at the University of Rhode Island College of Pharmacy, Kingston, R.I., said at the Interscience Conference on Antimicrobial Agents and Chemotherapy.

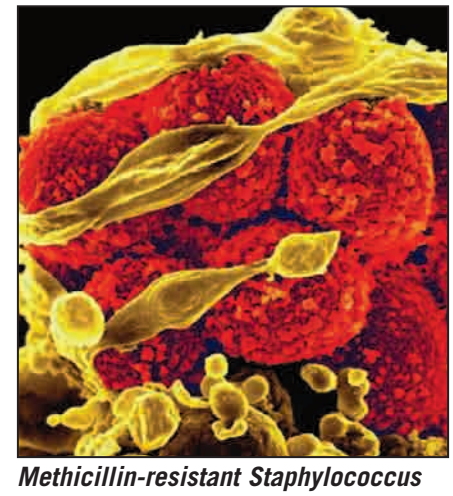
Maybe it was because vancomycin dosing is, in part, weight based and perhaps problematic for obese patients. Clinicians may be reluctant to exceed standard dosing even if BMIs suggest it, due to toxicity concerns; it's unclear if patients in the study received adequate doses.

Linezolid "is a little more straightforward. Maybe obese patients were more likely to get the right dose," Dr. Caffrey said.

She and her coinvestigators hope to look further into the antibiotic treatment of MRSA pneumonia in the overweight population.

The investigation was a subgroup analysis of a larger MRSA pneumonia comparison study that found nonobese patients treated with linezolid were less likely to have 30-day hospital readmissions (HR 0.60, 95% CI 0.37-0.97). There were no other outcome differences between the drugs. Patients in the study were treated for at least 3 days.

The conference was sponsored by the American Society for Microbiology. Pfizer and the Department of Veterans Affairs funded the study. Two of the researchers were Pfizer employees. Dr. Caffrey's research is funded in part by Pfizer. ■



COURTESY U.S. NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

***Methicillin-resistant Staphylococcus aureus* (MRSA) bacteria**

Smoking Relapse Deadly for Stroke Survivors

BY PATRICE WENDLING
IMNG Medical News

MUNICH – Patients who resume smoking after an ischemic stroke raise their risk of dying by roughly threefold within 1 year, a prospective, observational study has shown.

Moreover, the risk of dying increases the sooner the relapse occurs. Patients who resume smoking within 10 days of leaving the hospital are five times more likely to die within a year than are those who remain smoke free.

"Smoking relapse is extremely dangerous after an acute ischemic stroke," said Dr. Furio Colivicchi of the cardiovascular department at San Filippo Neri Hospital, Rome.

Cardiologists at San Filippo, in collaboration with neurologists from the Santa Lucia Foundation of Rome, enrolled 921 consecutive active smokers who ceased smoking after admission to the hospital for acute ischemic stroke and reported being motivated to continue abstaining once discharged.

All patients received a brief in-hospital smoking cessation counseling session lasting 5-20 minutes and delivered by trained nurses (73%) or physicians (27%).

Patients did not receive any specific postdischarge support or pharmacotherapy for smoking cessation. One-third of patients (34%), however, were referred to a hospital-based rehabilitation program after their stroke.

The cohort of 584 men and 337 women had an average National Institutes of Health Stroke Scale score of 9.1, 11% had had a previous stroke, 18% had a previous myocardial infarction, 69% had hypertension, and 20% were obese. Their average age was 67 years.

During the 12-month follow-up, 54% of all patients resumed regular cigarette smoking, with 50% relapsing within 3 weeks of discharge, Dr. Colivicchi reported at the annual congress of the European Society of Cardiology.

PATRICE WENDLING/IMNG MEDICAL MEDIA

Patients who smoke within 10 days of discharge are likely to die within 1 year, Dr. Furio Colivicchi said.

Patients who relapsed were significantly more likely to be older (69 years vs. 65 years) and female (44% vs. 28%), and were less likely to do so if referred to a hospital-based stroke rehabilitation program (25% vs. 44%), all highly significant differences.

During the 12-month follow-up, 89 patients (9.7%) died. Most of the deaths were due to ischemic events, both coronary and stroke recurrences, Dr. Colivicchi told the media at the meeting.

"The causal link between smoke and further ischemic events is complex," he said. "But we do know that smoking has a negative impact on the cardiovascular system, and it increases the ability of the platelets to aggregate, for instance, which is a crucial point in these ischemic syndromes."

After adjustment for confounding interactions including clinical variables and variables related to the acute event, a strong relationship was found between smoking relapse and all-cause mortality, Dr. Colivicchi said. The risk of death was 5.1-fold higher at 10 days, 3.8-fold higher at 120 days, and 2.6-fold higher at roughly 1 year.

A linear correlation exists between the number of cigarettes and the probability of suffering an acute cardiovascular event, but even small amounts, such as fewer than five cigarettes per day, have been linked to increased cardiovascular events, he noted. Most of the patients in the study were heavy smokers, smoking more than 10 cigarettes per day prior to the index event and typically relapsing to their original amount.

"We must be very careful and provide a more comprehensive approach because individual counseling is not fully effective if it is not followed by postdischarge support for this specific problem and possibly, in selected cases, by pharmacological treatment aimed at reducing the risk of relapse," he said.

A recent study in 4,834 patients with acute coronary syndrome (ACS) reported that while 20% were smokers at the time of their ACS, only 24% received any smoking intervention from their general practitioner within 3 months of the event. Of these, 9% received advice only and 15% received pharmacological intervention (Eur. J. Prev. Cardiol. 2012 Sept. 5 [epub ahead of print]).

Dr. Colivicchi reported having no relevant financial conflicts. ■

High-Dose Vitamin D Did Not Curb URTIs

BY MARY ANN MOON
IMNG Medical News

Monthly high-dose vitamin D supplementation failed to reduce the number of upper respiratory tract infections in healthy adults of European extraction who already had adequate serum 25-hydroxyvitamin D levels, according to a report in JAMA.

The treatment also failed to reduce the severity or duration of URTIs, or the number of days patients missed work, said Dr. David R. Murdoch of the department of pathology, University of Otago, Christchurch, New Zealand, and his associates (JAMA 2012;308:1333-9).

However, it is still possible that monthly high-dose vitamin D supplementation may prevent or ameliorate URTIs in other populations, the authors noted, particularly those with a high prevalence of vitamin D deficiency. And different regimens with smaller, steadier dosing might prove effective, they added.

Epidemiologic and observational studies have reported an association between low vitamin D levels and a high rate of a variety of respiratory tract infections. But the few clinical trials to examine the issue have been hampered by small study populations, short durations, and low doses of vitamin D.

This large, randomized, double-blind, placebo-controlled clinical trial was designed to overcome those drawbacks, the investigators said.

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For healthy adults, vitamin D was no help against the common cold.

Dr. Murdoch and his colleagues assessed 322 healthy adults with a mean age of 47 years, of whom 75% were women. The patients were randomly assigned to receive either oral vitamin D_3 or matching placebo tablets every month for 18 months, and were followed closely for signs and symptoms of URTIs. Nasopharyngeal swabs were collected and analyzed for the presence of 20 viruses whenever a patient developed a runny nose, nasal stuffiness, sore throat, or cough that was not attributed to allergy.

The active-treatment group received a loading dose of 200,000 IU of vitamin D_3 for months 1 and 2, then a maintenance dose of 100,000 IU for the remainder of the study. A total of 91% of the patients completed the study, and there were only three missed appointments throughout.

Serum levels of 25-hydroxyvitamin D rose dramatically in the patients who received active treatment but not in those who received placebo.

The main outcome measure of this study was the number of URTIs that developed during follow-up.

There were 593 URTIs in the vitamin D group, with a mean of 3.7 infections per person, and 611 URTIs in the placebo group, with a mean of 3.8 infections per person. This was not a statistically significant difference, the investigators said.

The results didn't change when the data were categorized according to patients' scores on the Wisconsin Upper Respiratory Symptom Survey 24, which measures the severity and functional impact of URTIs. Nor were outcomes altered by an analysis based on patients' serum vitamin D levels at baseline.

The lack of a treatment effect also persisted across one summer and two winter seasons, even though the number of URTIs nearly doubled during the winter. The mean number of URTIs was 1.3 for both study groups in summer, and 2.5 and 2.3 in winter for the placebo and treatment groups, respectively.

There also was no difference in URTI severity between patients who received vitamin D and those who received placebo. The number of URTIs associated with positive nasopharyngeal swabs also was not significantly different between the two groups.

Another measure of URTI severity – the percentage of patients who missed at least 1 day of work when sick with a cold – also was exactly the same, at 41% in both groups.

There were no cases of asymptomatic hypercalcemia and no other adverse events attributed to vitamin D supplementation. The number of serious adverse events was not significantly different between the active-treatment and placebo groups.

"Further research is required to clarify whether there is benefit from supplementation in other populations and with other dosing regimens," Dr. Murdoch and his associates concluded.

The trial was well powered to detect meaningful differences between the two study groups, boasted very good adherence to treatment assignments and a low dropout rate, and used a well-validated outcome tool to assess patients' signs and symptoms," said Dr. Jeffrey A. Linder in an editorial accompanying Dr. Murdoch's report (JAMA 2012; 308:1375-6).

"Not only did the treatment fail to decrease the rate of URTIs, but it also failed to show any impact on the severity, duration, or microbiologic characteristics of infections between the two study groups.

"Vitamin D should be added to the list of ineffective therapies for the common cold," he said.

This study was supported by the Health Research Council of New Zealand. No financial conflicts of interest were reported. ■

Tiotropium Limits Exacerbations

Poorly Controlled • *from page 1*

associates (N. Engl. J. Med. 2012 Sept. 3 [doi:10.1056/NEJMoa1208606]).

However, the improvements in forced expiratory volume in 1 second (FEV_1) were "relatively small (less than 10%)," and the number of symptom-free days did not differ between patients who received tiotropium and those who received placebo.

Moreover, the use of rescue medications was the same between the two groups, and patient ratings of asthma-related quality of life also were the same on two measures, the researchers noted.

Tiotropium is the most widely used long-acting anticholinergic inhaled bronchodilator in the world for the treatment of chronic obstructive pulmonary disease, but it has only recently been investigated as a potential adjunctive therapy for asthma.

Dr. Kerstjens and his colleagues assessed the drug's effects in two 48-week randomized, controlled trials conducted in 15 countries, both of which were funded by Boehringer Ingelheim and Pfizer. They presented their findings at the annual meeting of the European Respiratory Society simultaneously with publication.

The studies included 912 adults aged 18-75 years who had a 5-year or longer history of asthma and persistent airflow limitation despite self-reported daily use of inhaled glucocorticoids and LABAs. They were randomly assigned to self administer puffs of either tiotropium (237 patients in study 1 and 219 patients in study 2) or placebo (222 patients in study 1 and 234 patients in study 2) every morning as add-on therapy.

Patients were allowed to continue the use of stable doses of sustained-release theophylline, leukotriene modifiers, anti-immunoglobulin E antibody, or oral glucocorticoids, and were given open-label inhalers of salbutamol or albuterol for use as rescue medication.

The first two lung-function end points of both studies were the peak FEV_1 response and the trough FEV_1 response at week 24, expressed as the change from baseline FEV_1. Tiotropium topped placebo in peak FEV_1 response by an average of 86 mL in trial 1 and 154 mL in trial 2, differences that were significant.

The average difference in trough FEV_1 response between tiotropium and placebo groups was 88 mL in trial 1 and 111 mL in trial 2. Those differences were "relatively small" but also statistically significant.

"It should be noted that [these differences occurred] in patients who were already receiving a long-acting bronchodilator and had fixed airflow limitation," the investigators noted. The results also should be considered "in the context of the need for additional treatments for this patient population and the limitations of current alternatives," they added.

A third lung-function end point was the time until at least 25% of patients had their first severe exacerbation of asthma. That interval was 56 days longer with tiotropium (282 days), compared with placebo (226 days).

The number of severe exacerbations was a secondary end point of both trials. That number was 0.53 exacerbations per patient-year with tiotropium, significantly fewer than the 0.66 per patient-year with placebo.

In addition, 27% of patients in both tiotropium groups had at least one severe exacerbation, which was significantly less than the 33% rate in both placebo groups.

However, asthma-related quality of life did not differ significantly between tiotropium and placebo groups in either trial. The minimal clinically important difference between the two groups was not achieved when measured by both the Asthma Control Questionnaire 7 and the 32-item Asthma Quality of Life Questionnaire.

Similarly, daily symptom diaries showed "small or nonsignificant" differences between the active drug and the placebo groups in symptom-free days. And the use of rescue medications also was similar.

Adverse events occurred in 73.5% of the tiotropium group and 80.3% of the placebo group, and allergic rhinitis was the only one that occurred more often in the tiotropium group. Adverse events were judged to be treatment related in 5.7% of the tiotropium group and 4.6% of the placebo group.

Serious adverse events occurred in 8.1% of the tiotropium group and 8.8% of the placebo group. Three of those events – two asthma exacerbations and one cerebral infarction – occurred in the tiotropium group and were considered life threatening.

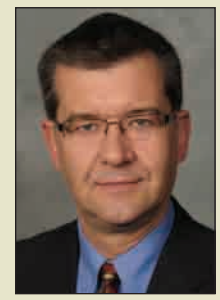
Cardiac events occurred in less than 2% of both study groups; they were considered drug related in 0.4% of patients in the tiotropium group and 0.2% of those in the placebo group. Adverse changes in blood pressure, pulse rate, laboratory measures, and electrocardiograms were balanced between the two study groups.

Less than 2% of all patients experienced dry mouth – a typical adverse event with anticholinergic agents – but it was reported more frequently in the tiotropium group (eight patients vs. three patients), Dr. Kerstjens and his associates said.

Dr. Kerstjens reported additional associations with Almirall, Chiesi, Novartis, and Nycomed, and his associates reported ties to numerous industry sources. ■

COMMENTARY

Dr. Darcy D. Marciniuk, FCCP, comments: The addition of a long-acting cholinergic in this select group of difficult to control adult asthma patients appears to have incremental benefit and be well tolerated in these two randomized-controlled studies. In these asthmatic subjects with persistently abnormal lung function despite being prescribed at least combination ICS/LABA (adherence was not objectively validated), once-daily tiotropium for 48 weeks led to modest improvements in lung function and time to next exacerbation. Increased adverse events and side-effects were not noted.



Stopping LABA Therapy May Worsen Controlled Asthma

BY MARY ANN MOON
IMNG Medical News

Withdrawing long-acting beta-agonist therapy worsened refractory asthma that had been controlled with a combination of LABAs and inhaled corticosteroids, according to a meta-analysis.

The findings run counter to the Food and Drug Administration's black-box warning that patients should reduce use of LABAs such as salmeterol or formoterol once they achieve asthma control.

Stopping LABAs after achieving asthma control was associated with reduced asthma control, increased symptom frequency, increased use of rescue bronchodilators, decreased asthma-related quality of life, and similar rates of adverse events and serious adverse events, compared with continuing LABAs in combination therapy, according to the meta-analysis' authors, who focused on the only five randomized, controlled clinical trials (RCTs) to examine this issue.

"Thus, in contrast to FDA recommendations of stepping off LABA therapy [once] asthma is controlled, our analysis supports the continued use of LABAs to maintain asthma control," Dr. Jan L. Brozek of the department of clinical epidemiology and biostatistics and medicine, McMaster University, Hamilton, Ont., and his associates wrote in Archives of Internal Medicine (Arch. Intern. Med. 2012 [doi:10.1001/archinternmed.2012.3250]).

However, they noted that this conclusion is based on the pooled results of only five studies, all of which had substantial limitations.

VITALS

Major Finding: Compared with combination LABA and inhaled corticosteroid therapy for controlled refractory asthma, LABA step-down therapy was associated with an average 0.24-point drop in quality of life scores for control of asthma, 9.2% fewer symptom-free days, and an average of 0.71 more puffs/day from a rescue bronchodilator.

Data Source: A meta-analysis of five randomized, controlled trials adolescents and adults with asthma who either stepped off LABA therapy (660 patients) or continued LABA therapy (682 patients) after achieving control.

Disclosures: This meta-analysis was supported by McMaster University, the AAAAI, and the American Thoracic Society. The researchers reported various industry ties.

The researchers undertook the meta-analysis because of the ongoing controversy over whether to withdraw or continue LABA therapy once asthma is adequately controlled, as the Food and Drug Administration recommends in a black-box warning for the drugs.

The five RCTs included in the meta-analysis were all sponsored by the manufacturers of the study drugs. Four were published in peer-reviewed journals, and one was a conference abstract. All the RCTs involved adolescents or adults with at least a 6-month history of mild to moderate asthma, but four of the five trials did not specify whether combined therapy with inhaled corticosteroids and LABAs had been required to control symptoms at enrollment.

Compared with continued combination therapy, LABA step-down therapy was associated with an average 0.24-point drop in Asthma Quality of Life Questionnaire scores for control of asthma, 9.2% fewer symptom-free days, and an average of 0.71 more puffs/day from a rescue bronchodilator.

Despite the meta-analysis results, the investigators cautioned that the duration of well-controlled asthma on combination therapy was shorter than the 3 months that are recommended to adequately judge the treatment effect. None of the RCTs reported emergency department visits, unscheduled office visits for asthma, days missed from work or school, costs, or complications associated with the corticosteroids, the authors said. All were of short duration, none provided information on treatment adherence, and some had high dropout rates.

Nevertheless, "our findings likely represent the current best evidence about stepping off LABA therapy in patients with asthma," the investigators asserted.

The pooled analysis showed "no statistically significant results for any of the reported asthma outcomes of interest showing a benefit from [the] LABA step-off approach, compared with continued use of the same dose of inhaled corticosteroids and LABA," Dr. Brozek and his associates said. ■

New Data Enlighten Update of OSAS Guidance

BY DOUG BRUNK
IMNG Medical News

An updated clinical practice guideline from the American Academy of Pediatrics spells out which children with obstructive sleep apnea syndrome who undergo adenotonsillectomy should be admitted as inpatients.

"That's really important because the vast majority of children have adenotonsillectomy on an outpatient basis," said Dr. Carole L. Marcus, who chaired a subcommittee that assembled the guideline, which was updated from a 2002 version and published in Pediatrics.

Another new component of the 10-page guideline, titled "Diagnosis and Management of Childhood Obstructive Sleep Apnea Syndrome," includes an option for clinicians to prescribe intranasal steroids for a subset of children with obstructive sleep apnea syndrome (OSAS).

"For children with mild obstructive sleep apnea – especially for those in whom surgery might be contraindicated, or in those who have already had surgery and have some residual obstructive apnea – intranasal steroids could be helpful," Dr. Marcus, who directs the Sleep Center at the Children's Hospital of Philadelphia, said in an interview. "There are still a lot of unanswered questions [about this practice], one of the biggest being that all of the studies have been relatively short term, meaning weeks to months, not years. Does a child need just one course, or do they need to be on it for the rest of their lives? Those are studies that need to be done."

Intranasal steroid: Does a child need just one course, or do they need to be on it forever?

DR. MARCUS

To update the 2002 guideline, Dr. Marcus and 11 other members of the interdisciplinary AAP Subcommittee on Obstructive Sleep Apnea Syndrome reviewed 3,166 articles from the medical literature related to the diagnosis and management of OSAS in children and adolescents that were published during 1999-2008. Then subcommittee members "selectively updated this literature search for articles published from 2008 to 2011 specific to guideline categories." Of the 3,166 studies, 350 were used to formulate eight recommendations, termed "key action statements" (Pediatrics 2012;130:576-84).

Since publication of the previous guideline, "there has been a huge amount of research done in this field," noted Dr. Marcus, who is also a professor of pediatrics at the University of Pennsylvania, Philadelphia. "Many of the initial studies we looked at for the first guideline were case series. Now people are doing well-structured studies and looking at some of the detailed outcomes such as neurocognitive findings."

The guideline recommends that the following subset of children be admitted as inpatients after tonsillectomy: those younger than age 3; those with severe OSAS on polysomnography; those with cardiac complications of OSAS; those with failure to thrive; those who are obese; and those with craniofacial anomalies, neuromuscular disorders, or a current respiratory infection.

Another component to the guideline is the recommendation that clinicians refer patients for continuous positive airway pressure (CPAP) management if OSAS signs and symptoms persist after adenotonsillectomy or if adenotonsillectomy is not performed. Dr. Marcus described CPAP as "the best way to go as a second-line option.."

One component of the guideline related to polysomnography proved difficult for the committee members and the consulting medical societies to reach consensus on. This recommendation states that clinicians should obtain a polysomnogram or refer the patient to a sleep specialist or otolaryngologist if the child or adolescent snores regularly or meets the symptoms and signs of OSAS.

"If one agrees that sleep studies are the only objective way to tell what's going on, we just don't have the resources in this country to study every child," Dr. Marcus said. "The literature is very strong showing that a history and physical exam could give you an idea of which children you should have an index of suspicion about, but do not tell you which children have sleep apnea. The vast number of children who have adenotonsillectomy for suspected OSA are having it done without any sort of objective finding. The studies that have been done show that about 50% of the time, even with a history that seems indicative of OSA, the children will have normal sleep studies."

Because of this quandary, the committee included a related recommendation, which reads that if polysomnography is not available, "then clinicians may order alternative diagnostic tests, such as nocturnal video recording, nocturnal oximetry, daytime nap polysomnography, or ambulatory polysomnography."

Dr. Marcus said that further changes to the new guideline may be warranted pending the results of the Childhood Adenotonsillectomy Study for Children With OSAS (CHAT). Sponsored by the National Heart, Lung, and Blood Institute, the goal of this multicenter, randomized trial is to determine the effect of adenotonsillectomy surgery on OSAS in children.

There is a 44-page technical report that details the procedures the subcommittee members followed and the data they considered (Pediatrics 2012;130:e714-55).

Dr. Marcus disclosed that she has received research support from Philips Respironics. Another subcommittee member, Dr. David Gozal, disclosed having research support from AstraZeneca and being a speaker for Merck.; Dr. Ann C. Halbower disclosed receiving research funding from Resmed; and Dr. Michael S. Schechter disclosed that he consults for to Genentech and Gilead, and that he has received research support from Mpex Pharmaceuticals, Vertex Pharmaceuticals, and other companies. ■

FDA: No Sildenafil for Kids With PAH

BY FRANCES CORREA
IMNG Medical News

The Food and Drug Administration is warning physicians not to use off-label Revatio (sildenafil) to treat pulmonary arterial hypertension in children younger than 18 years.

The FDA made the announcement after a pediatric trial revealed high doses of Revatio increased mortality, and low doses failed to improve exercise ability among young PAH patients.

Revatio is a phosphodiesterase-5 inhibitor approved by the FDA to improve exercise ability and delay the progression of PAH in adults. However, the drug is not approved for treatment in children.

Results from a recent randomized, controlled study of Revatio use in 234 children aged 1-17 years with mild to moderate PAH demonstrated that low doses of the drug didn't improve patients' exercise ability.

In addition, the mortality rate among children taking high doses of Revatio was 3.5 times greater than that of children taking low doses, a statistically significant difference.

The FDA has added a warning to Revatio's labeling stating that the drug is not recommended for pediatric patients. The agency also has required the drug's manufacturer, Pfizer, to evaluate Revatio's mortality risk in adults. Physicians can report adverse side effects to the FDA's MedWatch program at fda.gov/SafetyMedWatch/. ■

Budesonide Reduces Adult Height

Asthma • *from page 1*

budesonide were a mean of 0.8 cm shorter than men who took placebo as children.

During the first 2 years of the CAMP trial, rates of growth had already slowed, showing a 1.3-cm difference between the budesonide and placebo groups. At the end of that trial, the difference was 1.2 cm, a deficit that did not change as the patients entered young adulthood.

Final height was related to daily dosage during the randomized trial, with a decrement of 0.1 cm for each microgram per kilogram of budesonide. Several baseline characteristics were also significantly related to lower adult height, including Hispanic ethnicity and being female, or having a higher Tanner stage, greater body mass index, longer duration of asthma, and low vitamin D levels.

VITALS

Major Finding: Adults who took 400 mcg of budesonide daily as children were more than 1 cm shorter than those who took nedocromil or placebo.

Data Source: The 8-year observational study included 943 patients who had participated in the Childhood Asthma Management Program trial.

Disclosures: The CAMP trial and its observational study were funded by the National Heart, Lung, and Blood Institute and the National Center for Research Resources. Dr. Kelly serves on steering committees for and has received consulting fees from AstraZeneca, GlaxoSmithKline, and other companies. His coauthors also reported multiple financial relationships with pharmaceutical companies.

Since the CAMP trial concluded, research has shown that 200 mcg/day budesonide in a dry-powder inhaler is sufficient to control mild to moderate asthma and prevent exacerbations in children.

"Even at this lower dose, there was a reported mean reduction of 1.0 cm in height during the first 2 years of therapy," the investigators noted.

"Although the systemic effects of inhaled glucocorticoids are dose dependent, they are also dependent on the therapeutic index of the specific inhaled glucocorticoid and the delivery device used. Thus, it seems prudent to select inhaled glucocorticoids and devices with higher therapeutic indexes, and to use them in the lowest effective doses in children with persistent asthma."

Ultimately, they concluded, parents and physicians must work together to decide the risk-benefit ratio that is most appropriate and acceptable for each individual patient.

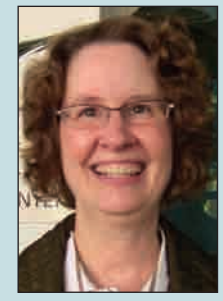
"In the information about inhaled glucocorticoids and their side effects that is provided to parents, the potential effect on adult height must be balanced against the large and well-established benefits of these drugs in controlling persistent asthma," concluded Dr. Kelly of the University of New Mexico, Albuquerque, and his coauthors.

The CAMP trial and its observational study were funded by the National Heart, Lung, and Blood Institute and the National Center for Research Resources.

Dr. Kelly serves on steering committees for and has received consulting fees from AstraZeneca, GlaxoSmithKline, and other companies. His coauthors reported that they have multiple financial relationships with pharmaceutical companies. ■

COMMENTARY

Dr. Susan Millard, FCCP, comments: This NEJM article is important for all physicians caring for children. But the final question for every physician and parent: How do we balance the risk of airway remodeling, the economic and educational burden related to loss of work and school, risk of death from an asthma exacerbation with being 0.47 in (1.2 cm) shorter as an adult?



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INDICATION

BROVANA is indicated for the long term, twice daily (morning and evening) maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. BROVANA is for use by nebulization only.

IMPORTANT SAFETY INFORMATION

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another long-acting beta$_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including arformoterol, the active ingredient in BROVANA (see WARNINGS). The safety and efficacy of BROVANA in patients with asthma have not been established. All LABA, including BROVANA, are contraindicated in patients with asthma without use of a long-term asthma control medication (see CONTRAINDICATIONS).

Please see the Brief Summary of Prescribing Information on the following pages for additional Important Safety Information.

Please visit **www.brovana.com** for full Prescribing Information.

References: 1. Baumgartner RA, Hanania NA, Calhoun WJ, Sahn SA, Sciarappa K, Hanrahan JP. Nebulized arformoterol in patients with COPD: a 12-week, multicenter, randomized, double-blind, double-dummy, placebo- and active-controlled trial. *Clin Ther*. 2007;29(2):261-278. **2.** BROVANA [prescribing information]. Marlborough, MA: Sunovion Pharmaceuticals Inc; 2012.

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FOR ORAL INHALATION ONLY

BRIEF SUMMARY

WARNING: ASTHMA RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another long-acting beta$_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including arformoterol, the active ingredient in BROVANA (see WARNINGS). The safety and efficacy of BROVANA in patients with asthma have not been established. All LABA, including BROVANA, are contraindicated in patients with asthma without use of a long-term asthma control medication (see CONTRAINDICATIONS).

INDICATIONS AND USAGE

BROVANA (arformoterol tartrate) Inhalation Solution is indicated for the long-term, twice daily (morning and evening) maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. BROVANA is for use by nebulization only.

CONTRAINDICATIONS

BROVANA (arformoterol tartrate) Inhalation Solution is contraindicated in patients with a history of hypersensitivity to arformoterol, racemic formoterol or to any other components of this product.

All LABA, including BROVANA, are contraindicated in patients with asthma without use of a long-term asthma control medication. (see **WARNINGS**).

WARNINGS

- **ASTHMA RELATED DEATH**

  Long-acting beta$_2$-adrenergic agonists may increase the risk of asthma-related death. The safety and efficacy of BROVANA in patients with asthma have not been established. All LABA, including BROVANA, are contraindicated in patients with asthma without use of a long-term asthma control medication (see CONTRAINDICATIONS).
  - A 28-week, placebo-controlled US study comparing the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13, 176 in patients treated with salmeterol vs. 3/13, 179 in patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). The increased risk of asthma-related death may represent a class effect of the long-acting beta$_2$-adrenergic agonists, including BROVANA. No study adequate to determine whether the rate of asthma related death is increased in patients treated with BROVANA has been conducted.
  - Clinical studies with racemic formoterol (Foradil® Aerolizer™) suggested a higher incidence of serious asthma exacerbations in patients who received racemic formoterol than in those who received placebo. The sizes of these studies were not adequate to precisely quantify the differences in serious asthma exacerbation rates between treatment groups.
- **The studies described above enrolled patients with asthma. Data are not available to determine whether the rate of death in patients with COPD is increased by long-acting beta$_2$-adrenergic agonists.**
- **BROVANA is indicated for the long term, twice daily (morning and evening) maintenance treatment for bronchoconstriction in chronic obstructive pulmonary disease (COPD), and is not indicated for the treatment of acute episodes of bronchospasm, i.e., rescue therapy.**
- **BROVANA should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. The use of BROVANA in this setting is inappropriate.**
- **BROVANA should not be used in children as the safety and efficacy of BROVANA have not been established in pediatric patients.**
- **BROVANA should not be used in conjunction with other inhaled, long-acting beta$_2$-agonists. BROVANA should not be used with other medications containing long-acting beta$_2$-agonists.**
- **When beginning treatment with BROVANA, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms.**
- **See PRECAUTIONS and Information for Patients.**

Paradoxical Bronchospasm

As with other inhaled beta$_2$-agonists, BROVANA can produce paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, BROVANA should be discontinued immediately and alternative therapy instituted.

Deterioration of Disease

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If BROVANA no longer controls the symptoms of bronchoconstriction, or the patient's inhaled, short-acting beta$_2$-agonist becomes less effective or the patient needs more inhalation of short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dosage of BROVANA beyond the recommended 15 mcg twice daily dose is not appropriate in this situation.

Cardiovascular Effects

BROVANA, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of BROVANA at the recommended dose, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QT_c interval, and ST segment depression. The clinical significance of these findings is unknown. BROVANA, as with other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension (see **PRECAUTIONS, General**).

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of BROVANA as demonstrated by cases of anaphylactic reaction, urticaria, angioedema, rash and bronchospasm.

Do Not Exceed Recommended Dose

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. As with other inhaled beta$_2$-adrenergic drugs, BROVANA should not be used more often, at higher doses than recommended, or with other long-acting beta-agonists.

PRECAUTIONS

General

BROVANA (arformoterol tartrate) Inhalation Solution should not be used to treat acute symptoms of COPD. BROVANA has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. When prescribing BROVANA, the physician should also provide the patient with an inhaled, short-acting beta$_2$-agonist for treatment of COPD symptoms that occur acutely, despite regular twice-daily (morning and evening) use of BROVANA. Patients should also be cautioned that increasing inhaled beta$_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated (see **Information for Patients**).

BROVANA, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and/or diastolic blood pressure, pulse rate and electrocardiograms have been seen infrequently in individual patients in controlled clinical studies with arformoterol tartrate. Doses of the related beta$_2$-agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

Beta-agonist medications may produce significant hypokalemia in some patients, possibly though intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.

Clinically significant changes in blood glucose and/or serum potassium were infrequent during clinical studies with long-term administration of BROVANA at the recommended dose.

Information for Patients

Patients should be instructed to read the accompanying Medication Guide with each new prescription and refill. Patients should be given the following information:

1. Patients should be informed that long-acting beta$_2$-adrenergic agonists, such as BROVANA, increase the risk of asthma-related death. All LABA, including BROVANA, are contraindicated in patients with asthma without use of a long-term asthma control medication (see **CONTRAINDICATIONS**).
2. BROVANA is not indicated to relieve acute respiratory symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting, beta$_2$-agonist (the health-care provider should prescribe the patient with such medication and instruct the patient in how it should be used). Patients should be instructed to seek medical attention if their symptoms worsen, if BROVANA treatment becomes less effective, or if they need more inhalations of a short-acting beta$_2$-agonist than usual. Patients should not inhale more than one dose at any one time. The daily dosage of BROVANA should not exceed one ready-to-use vial (15 mcg) by inhalation twice daily (30 mcg total daily dose).
3. Patients should be informed that treatment with beta$_2$-agonists may lead to adverse events which include palpitations, chest pain, rapid heart rate, tremor, or nervousness.
4. Patients should be instructed to use BROVANA by nebulizer only and not to inject or swallow this inhalation solution.
5. Patients should protect BROVANA ready-to-use vials from light and excessive heat. The protective foil pouches should be stored under refrigeration between 2ºC and 8ºC (36º–46ºF). They should not be used after the expiration date stamped on the container. After opening the pouch, unused ready-to-use vials should be returned to, and stored in, the pouch. An opened ready-to-use vial should be used right away. Discard any ready-to-use vial if the solution is not colorless.
6. The drug compatibility (physical and chemical), efficacy and safety of BROVANA when mixed with other drugs in a nebulizer have not been established.
7. Women should be advised to contact their physician if they become pregnant or if they are nursing.
8. It is important that patients understand how to use BROVANA appropriately and how it should be used in relation to other medications to treat COPD they are taking.

Drug Interactions

If additional adrenergic drugs are to be administered by any route, they should be used with caution because the pharmacologically predictable sympathetic effects of BROVANA may be potentiated.

When paroxetine, a potent inhibitor of CYP2D6, was co-administered with BROVANA at steady-state, exposure to either drug was not altered. Dosage adjustments of BROVANA are not necessary when the drug is given concomitantly with potent CYP2D6 inhibitors.

Concomitant treatment with methylxanthines (aminophylline, theophylline), steroids, or diuretics may potentiate any hypokalemic effect of adrenergic agonists.

The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the co-administration of beta-agonists with non-potassium sparing diuretics.

BROVANA, as with other beta$_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QT_c interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QT_c interval have an increased risk of ventricular arrhythmias. The concurrent use of intravenously or orally administered methylxanthines (e.g., aminophylline, theophylline) by patients receiving BROVANA has not been completely evaluated. In two combined 12-week placebo controlled trials that included BROVANA doses of 15 mcg twice daily, 25 mcg twice daily, and 50 mcg once daily, 54 of 873 BROVANA-treated subjects received concomitant theophylline at study entry. In a 12-month controlled trial that included a 50 mcg once daily BROVANA dose, 30 of the 528 BROVANA-treated subjects received concomitant theophylline at study entry. In these trials, heart rate and systolic blood pressure were approximately 2-3 bpm and 6-8 mm Hg higher, respectively, in subjects on concomitant theophylline compared with the overall population.

Beta-adrenergic receptor antagonists (beta-blockers) and BROVANA may interfere with the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in COPD patients. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies were conducted in mice using oral administration and rats using inhalation administration to evaluate the carcinogenic potential of arformoterol.

In a 24-month carcinogenicity study in CD-1 mice, arformoterol caused a dose-related increase in the incidence of uterine and cervical endometrial stromal polyps and stromal cell sarcoma in female mice at oral doses of 1 mg/kg and above (AUC exposure approximately 70 times adult exposure at the maximum recommended daily inhalation dose).

In a 24-month carcinogenicity study in Sprague-Dawley rats, arformoterol caused a statistically significant increase in the incidence of thyroid gland c-cell adenoma and carcinoma in female rats at an inhalation dose of 200 mcg/kg (AUC exposure approximately 130 times adult exposure at the maximum recommended daily inhalation dose). There were no tumor findings with an inhalation dose of 40 mcg/kg (AUC exposure approximately 55 times adult exposure at the maximum recommended daily inhalation dose).

Arformoterol was not mutagenic or clastogenic in the following tests: mutagenicity tests in bacteria, chromosome aberration analyses in mammalian cells, and micronucleus test in mice.

Arformoterol had no effects on fertility and reproductive performance in rats at oral doses up to 10 mg/kg (approximately 2700 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis).

Pregnancy: Teratogenic Effects

Pregnancy Category C

Arformoterol has been shown to be teratogenic in rats based upon findings of omphalocele (umbilical hernia), a malformation, at oral doses of 1 mg/kg and above (AUC exposure approximately 370 times adult exposure at the maximum recommended daily inhalation dose). Increased pup loss at birth and during lactation and decreased pup weights were observed in rats at oral doses of 5 mg/kg and above (AUC exposure approximately 1100 times adult exposure at the maximum recommended daily inhalation dose). Delays in development were evident with an oral dose of 10 mg/kg (AUC exposure approximately 2400 times adult exposure at the maximum recommended daily inhalation dose).

Arformoterol has been shown to be teratogenic in rabbits based upon findings of malpositioned right kidney, a malformation, at oral doses of 20 mg/kg and above (AUC exposure approximately 8400 times adult exposure at the maximum recommended daily inhalation dose). Malformations including brachydactyly, bulbous aorta, and liver cysts were observed at doses of 40 mg/kg and above (approximately 22,000 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women. BROVANA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Labor and Delivery

There are no human studies that have investigated the effects of BROVANA on preterm labor or labor at term. Because beta-agonists may potentially interfere with uterine contractility, BROVANA should be used during labor and delivery only if the potential benefit justifies the potential risk.

Nursing Mothers

In reproductive studies in rats, arformoterol was excreted in the milk. It is not known whether arformoterol is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BROVANA is administered to a nursing woman.

Pediatric

BROVANA is approved for use in the long term maintenance treatment of bronchoconstriction associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema. This disease does not occur in children. The safety and effectiveness of BROVANA in pediatric patients have not been established.

Geriatric

Of the 873 patients who received BROVANA in two placebo-controlled clinical studies in adults with COPD, 391 (45%) were 65 years of age or older while 96 (11%) were 75 years of age or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Among subjects age 65 years and older, 129 (33%) received BROVANA at the recommended dose of 15 mcg twice daily, while the remainder received higher doses. ECG alerts for ventricular ectopy in patients 65 to ≤75 years of age were comparable among patients receiving 15 mcg twice daily, 25 mcg twice daily, and placebo (3.9%, 5.2%, and 7.1%, respectively).

A higher frequency (12.4%) was observed when BROVANA was dosed at 50 mcg once daily. The clinical significance of this finding is not known. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Experience in Adult Patients with COPD

Of the 1,456 COPD patients in the two 12-week, placebo-controlled trials, 288 were treated with BROVANA (arformoterol tartrate) Inhalation Solution 15 mcg twice daily and 293 were treated with placebo. Doses of 25 mcg twice daily and 50 mcg once daily were also evaluated. The numbers and percent of patients who reported adverse events were comparable in the 15 mcg twice daily and placebo groups.

The following table shows adverse events where the frequency was greater than or equal to 2% in the BROVANA 15 mcg twice daily group and where the rates of adverse events in the BROVANA 15 mcg twice daily group exceeded placebo. Ten adverse events demonstrated a dose relationship: asthenia, fever, bronchitis, COPD, headache, vomiting, hyperkalemia, leukocytosis, nervousness, and tremor.

CAP Guidelines: All About Pneumococcus

BY BRUCE JANCIN
IMNG Medical News

VAIL, COLO. – A major theme running through the latest guidelines for management of community-acquired pneumonia in children is that *Streptococcus pneumoniae* is the most common bacterial pathogen – and the best target for empiric therapy.

"It's really all about pneumococcus," declared Dr. Mark J. Abzug, professor of pediatrics at the University of Colorado, Denver.

The guidelines put forth jointly by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America endorse high-dose amoxicillin as first-line therapy for previously healthy, appropriately immunized infants, preschoolers, school-aged children, and adolescents with mild to moderate community-acquired pneumonia (CAP) of suspected bacterial origin (Clin. Infect. Dis. 2011; 53: e25-76).

High-dose oral amoxicillin at 90 mg/kg per day covers 87%-95% of *S. pneumoniae* isolates nationally, whereas most second- and third-generation oral cephalosporins cover only 60%-70%. Azithromycin isn't recommended for suspected pneumococcal CAP because of an associated resistance rate of up to 40%. Amoxicillin/clavulanic acid offers no incremental benefit over amoxicillin alone for pneumococcus, Dr. Abzug observed at the conference, which was sponsored by Children's Hospital Colorado.

Amoxicillin is recommended as first-line therapy in management of uncomplicated CAP.

DR. ABZUG

The guidelines recommend b.i.d. dosing of amoxicillin based largely on extrapolation from experience in acute otitis media. But Dr. Abzug takes issue with that guidance.

"I'm going to beg to differ with that recommendation and suggest that for pneumonia, which is a bit different from otitis, dividing t.i.d. is going to be better," he asserted.

Modeling studies indicate b.i.d. dosing of amoxicillin at 90 mg/kg per day is effective for 99% of highly susceptible (minimal inhibitory concentration of 0.5 mcg/mL) *S. pneumococcus* isolates, but only for 65% of strains with a minimum inhibitory concentration (MIC) of 2 mcg/mL, whereas t.i.d. dosing is sufficient for 90% of such strains.

For patients with nonserious amoxicillin allergies, the guidelines recommend cefuroxime, cefprozil, or cefpodoxime as oral alternatives; nationally, 67%-80% of *S. pneumoniae* strains are susceptible to these agents.

Clindamycin is an alternative option. Levofloxacin and linezolid are effective for close to 100% of isolates, but are best reserved for second- or third-line therapy.

The guidelines also recommend against routine complete blood counts, blood cultures, and urinary antigen detection tests in outpatients.

In fully immunized children with suspected bacterial CAP sufficiently serious for hospitalization, the recommendation is for parenteral ampicillin or penicillin G so long as local epidemiologic data indicate a lack of substantial resistance for invasive pneumococci as defined by an MIC greater than 8 mcg/mL and the patient doesn't have empyema or other potentially life-threatening complications. When those conditions aren't met, however, the guidelines endorse the third-generation cephalosporins ceftriaxone or cefotaxime.

Dr. Abzug applauded a recent study by a team at Children's Mercy Hospitals and Clinics in Kansas City, Mo., that provided support in everyday clinical practice for the ampicillin-first management strategy recommended in the national guidelines. The retrospective study included 1,033 patients admitted with CAP to the tertiary referral hospital during the 12 months before and after the 2008 introduction of a clinical practice guideline encouraging the use of ampicillin as the first-line empiric antibiotic in previously healthy children with uncomplicated CAP.

Prior to introduction of the hospital guideline, ceftriaxone was prescribed as empiric therapy for CAP in 72% of cases, with ampicillin being the second most commonly prescribed antibiotic at 13%. In the year after the guideline was introduced, ampicillin was the most common antibiotic, prescribed in 63% of cases, with ceftriaxone prescribed in 21%. And even though the prevalence of *S. pneumoniae* isolates with intermediate susceptibility or resistance to penicillin was 24% at the hospital during that time period, the change in therapy didn't result in an increase in adverse outcomes: The preguideline treatment failure rate was 1.5% and the postguideline rate was similar at 1% (Pediatrics 2012;129:e597-604).

He reported having no relevant financial conflicts. ■

Hyponatremia Raises Post–Elective Surgery Death Risk

Condition may reflect presence of comorbidities that lead to increased mortality.

BY JENNIE SMITH
IMNG Medical News

An observational study of nearly 1 million adults undergoing major surgery has found that those with hyponatremia saw a 44% increased risk of death within 30 days of surgery, compared with subjects without the disorder.

Hyponatremia is already a known negative prognostic factor in heart failure, liver disease, kidney disease, and pneumonia. The new study, published online in Archives of Internal Medicine (doi:10.1001/archinternmed.2012.3992), marks the first time that hyponatremia has been linked to higher risk of postsurgical mortality. Patients with any degree of hyponatremia before surgery saw a 5.2% risk of death, compared with 1.3% for patients without the disorder, even after the researchers adjusted for potential confounders (adjusted odds ratio 1.44; 95% confidence interval 1.38-1.50).

Adding to this stark finding was the fact that among patients undergoing elective surgery, the mortality risk associated with hyponatremia was even higher (aOR 1.59; 95% CI 1.50-1.69) and more pronounced still among a subgroup of subjects considered the healthiest preoperative candidates, those with a class 1 or 2 status according to American Society of Anesthesiologists criteria (aOR 1.93; 1.57-2.36).

For their research, investigators Dr. Alexander A. Leung of Brigham and Women's Hospital, Boston, and his colleagues, identified 964,263 adults undergoing major surgery from more than 200 hospitals between from January 2005 through December 2010 and evaluated their 30-day perioperative outcomes. Presurgery serum sodium levels were available for all patients included in the study.

Hyponatremia, defined as a serum sodium level of less than 135 mEq/L, occurred in 7.8% of all study patients, with 89% of these cases classified as "mild."

Dr. Leung and his colleagues wrote that their findings show that even mild hyponatremia preceding surgery is "not inconsequential and should not be ignored." In addition to the increased mortality risk, the investigators also found the presence of hyponatremia to be associated with significantly increased risk of morbidity, including major coronary events (1.8% vs. 0.7%; aOR 1.21; 95% CI 1.14-1.29), wound infections (7.4% vs. 4.6%; 1.24; 1.20-1.28), and pneumonia (3.7% vs. 1.5%; 1.17; 1.12-1.22).

Also, median length of hospital stay was prolonged by approximately 1 day among subjects with hyponatremia.

Dr. Leung and his colleagues wrote in their analysis that further research was needed to clarify whether hyponatremia caused adverse events or whether it merely indicated the presence of other serious underlying conditions contributing to morbidity and mortality.

The authors stopped short of making explicit clinical recommendations about correcting hyponatremia when it is detected prior to surgery.

Inducing rapid changes to sodium levels in a short period of time "can be potentially disastrous," the investigators wrote. However, "if monitored correction of hyponatremia is found to be safe and beneficial, it would strengthen causal inference and would be transformative to routine care since serum sodium is not presently recognized as an independent and reversible risk factor for perioperative complications."

The investigators noted among the weaknesses of their study its observational design, the potential existence of unmeasured confounders, and a lack of medication data that did not allow them to determine how risk may vary according to different drug exposures.

The study was supported in part by Alberta Innovates–Health Solutions and the Canadian Institutes for Health Research. They reported having no relevant conflicts of interest. ■

COMMENTARY

Dr. Lary Robinson, FCCP, comments: Dr. Leung and associates reviewed the SEER national hospitalization database of 964,263 patients undergoing surgery in 2005-2011 in the U.S., finding that 7.8% of patients had a baseline serum sodium less than 135. Taken as a group, the pre-op hyponatremia group had a significantly higher operative mortality (5.2%) than patients with a normal preop serum sodium (1.3%), suggesting that this blood value should signal the need to more carefully evaluate the patient's comorbidities prior to elective surgery and potentially correct the serum sodium. The authors felt that it was unclear "whether hyponatremia caused adverse events or whether it merely indicated the presence of other serious underlying conditions contributing to morbidity and mortality."

Common causes of baseline hyponatremia include the use of certain medications such as thiazide diuretics (hyponatremia is seen in 30% of patients who use thiazides), as well as chronic cardiac, liver, or renal disease. Although most anesthesiologists will not proceed with elective surgery with a serium sodium less than 130, even mild hyponatremia (serum sodium 130-134) can result in serious hyponatremia postop if the rather standard perioperative D5/1/2 normal saline + 20 KCl/L maintenance fluids are used indiscriminately. Preoperative hyponatremia is a red flag for the surgeon mandating a need for additional medical evaluation of the patient prior to surgery and a warning for extra-vigilent postop care.

Operative Error Skews Surgeons' Life-Support Decisions

BY MARK S. LESNEY
IMNG Medical News

Surgeons are more reluctant to withdraw life support if they made an error during surgery. This is especially true after an elective procedure, according to an extended analysis of a recent scenario-based survey of 2,100 surgeons who were involved in high-risk operations.

The survey included a series of questions regarding specialty-specific scenarios for 700 vascular surgeons (elective and emergent thoracoabdominal aortic aneurysm repair), 700 cardiothoracic surgeons (elective and emergent ascending aortic aneurysm repair), and 700 neurosurgeons (elective and emergent calcified right middle cerebral artery aneurysm clipping), according to Dr. Margaret L. Schwarze of the University of Wisconsin, Madison, and colleagues.

The three specialties were chosen based on the presumption of routine high-risk operations (Ann. Surg. 2012;256:10-5).

This analysis follows an earlier report in the Annals of Surgery by these same authors, who used these same survey data to determine that the majority of these surgeons performing high-risk operations did not discuss advanced directives with their patients, and 54% were unlikely to operate on these patients if they were aware of such directives prior to surgery (Ann. Surg. 2012;255:418-23).

Of the original 2,100 surveys that were sent out, 912 were completed and returned, with roughly equal percentages (54%-56%) for each specialty.

Multivariate analysis showed that surgeons who faced complications after emergency surgery that were not clearly the result of surgeon error were nearly twice as likely to agree to withdraw life-sustaining support, compared with surgeons evaluating elective procedures that had a complication resulting from surgeon error (odds ratio 1.95).

In addition, the odds of withdrawing life support were significantly greater among surgeons who were not optimistic about the patient's future quality of life (OR 1.75) and among those who were not concerned that the patients did not accurately value their future health state (OR 1.59), compared with their counterparts, the authors wrote in The Annals of Surgery.

"Iatrogenic complications that clearly derive from technical errors during elective procedures may pose considerable guilt and emotional burden upon surgeons," the authors speculated.

"It is understandable that such factors should weigh on the surgeon. However, our findings call into question the degree to which these factors may unduly interfere with a patient's ability to control his or her health care decisions."

In addition, "our data suggest that the commission of an error in surgical technique and prognostic optimism may present a challenge to patient autonomy. ... [This] suggests the importance of efforts to alleviate surgeons' emotional strain while simultaneously respecting the fierce ethic of responsibility that surgeons possess for patients' outcomes."

The authors reported that they had no financial disclosures. ■

COMMENTARY

Dr. Lary Robinson, FCCP, comments: Dr. Schwarze and associates surveyed 2100 vascular surgeons, cardiaothoracic surgeons, and neurosurgeons (912 replies) to assess their clinical responses to hypothethical elective and emergent surgical cases that resulted in a perioperative stroke. As with any multiple-answer survey, there are obviously limited potential responses. Based on the results, the authors speculated that surgeons who felt they made a technical error in elective surgery with a resultant stroke were more likely to disregard the patient's advance directives to withdraw life support.

Caution is advised, based on this survey interpretation, in assuming surgeons will overlook their ethical obligations if they think there was a technical error at surgery. A complication of any kind after an operative procedure weighs heavily on the surgeon, most of whom mentally review the case repeatedly to assess whether the complication resulted from an error in judgement, an error in technique, or was the result of patient disease. Whatever the cause, surgical ethics and patient wishes take precedence over everything else for the vast majority of surgeons, despite the interpretation of the results of this hypothetical survey."

New

DYMISTA™ (azelastine hydrochloride and fluticasone propionate) Nasal Spray 137 mcg/50 mcg per Spray

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Indication

Dymista Nasal Spray, containing an H_1-receptor antagonist and a corticosteroid, is indicated for the relief of symptoms of seasonal allergic rhinitis in patients 12 years of age and older who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief.

Important Risk Information

- Patients may experience somnolence. Caution patients against engaging in hazardous occupations requiring complete mental alertness, such as driving or operating machinery
- Patients should avoid concurrent use of alcohol or other central nervous system (CNS) depressants because additional reductions in alertness and additional impairment of CNS performance may occur
- Because of the inhibitory effect of corticosteroids on wound healing, avoid use in patients with recent nasal ulcers, nasal surgery, or nasal trauma until healed
- Glaucoma, cataracts, and increased intraocular pressure may be associated with nasal corticosteroid use; therefore, close monitoring is warranted in patients with a change in vision and/or with a history of increased intraocular pressure, glaucoma, and/or cataracts
- Patients using corticosteroids may be susceptible to infections and may experience a more serious or even fatal course of chicken pox or measles. Dymista should be used with caution in patients with active or quiescent tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex
- Systemic corticosteroid effects, such as hypercorticism and adrenal suppression, may occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue Dymista gradually, under medical supervision
- Potent inhibitors of cytochrome P450 (CYP) 3A4 may increase blood levels of fluticasone propionate
- Ritonavir: coadministration is not recommended
- Other potent CYP3A4 inhibitors, such as ketoconazole: use caution with coadministration
- Intranasal corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth routinely of pediatric patients receiving Dymista
- In clinical trials, the most common adverse reactions that occurred with Dymista Nasal Spray, azelastine hydrochloride nasal spray, fluticasone nasal spray, and vehicle placebo groups, respectively, were dysgeusia (4%, 5%, 1%, <1%), epistaxis (2% for each group), and headache (2%, 2%, 2%, and 1%)
- Pregnancy Category C: based on animal data; may cause fetal harm

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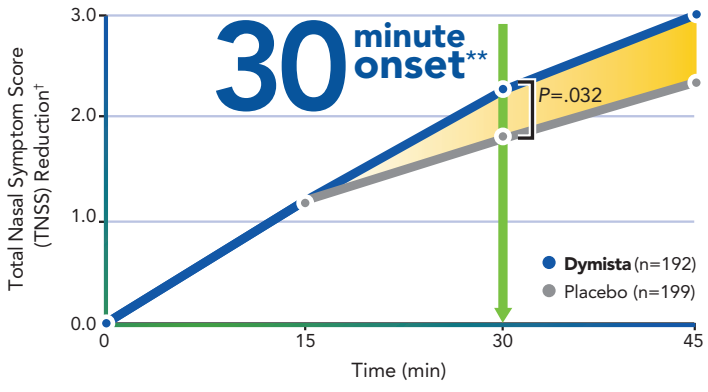
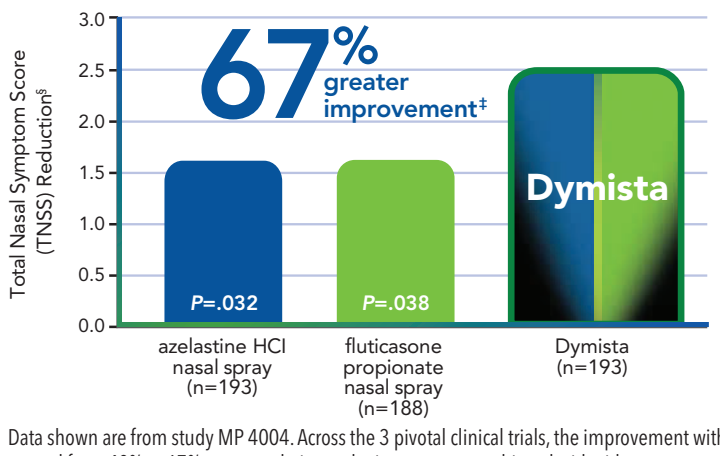


Magnitude of Nasal Symptom Relief Relative to azelastine HCl and to fluticasone propionate*[1,2]



Data shown are from study MP 4004. Across the 3 pivotal clinical trials, the improvement with Dymista ranged from 40% to 67% greater relative to the improvement achieved with either comparator.[1,2]

*As listed in the Full Prescribing Information, in 3 pivotal trials, symptom relief was measured by change from baseline in Total Nasal Symptom Score (TNSS) averaged over the 14-day study period. Dymista provided a statistically significant improvement in TNSS compared with both azelastine hydrochloride (HCl) and fluticasone propionate. The azelastine HCl and fluticasone propionate comparators used the same device and vehicle as Dymista and are not commercially marketed. Additionally, Dymista provided a statistically significant, rapid improvement in TNSS as early as 30 minutes after administration when compared with placebo.[1]

**Data shown are from study MP 4004. Onset of action was defined as the first timepoint at which Dymista was statistically superior to placebo in the mean change from baseline in instantaneous TNSS and was sustained thereafter.[1]

†Change from baseline in instantaneous TNSS following administration.[2]

‡Percent difference represents the improvement in TNSS with Dymista relative to azelastine HCl or fluticasone propionate comparator.[2]

§Change from baseline in the placebo-subtracted mean TNSS for each day (maximum score 24), averaged over the 14-day study period.[2]

References: 1. Dymista [package insert]. Somerset, NJ: Meda Pharmaceuticals Inc; 2012.
2. Data on File. Meda Pharmaceuticals Inc.

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

DYMISTA™

(azelastine hydrochloride and fluticasone propionate) Nasal Spray 137 mcg/50 mcg per Spray

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DYMISTA (AZELASTINE HYDROCHLORIDE 137 MCG / FLUTICASONE PROPIONATE 50 MCG) NASAL SPRAY

Brief Summary (for Full Prescribing Information, see package insert)

1 INDICATIONS AND USAGE

Dymista Nasal Spray is indicated for the relief of symptoms of seasonal allergic rhinitis in patients 12 years of age and older who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief.

5 WARNINGS AND PRECAUTIONS

5.1 Somnolence

In clinical trials, the occurrence of somnolence has been reported in some patients (6 of 853 patients) taking Dymista Nasal Spray [*see Adverse Reactions (6.1)*]. Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and motor coordination such as operating machinery or driving a motor vehicle after administration of Dymista Nasal Spray. Concurrent use of Dymista Nasal Spray with alcohol or other central nervous system depressants should be avoided because additional reductions in alertness and additional impairment of central nervous system performance may occur [*see Drug Interactions (7.1)*].

5.2 Local Nasal Effects

In clinical trials of 2 to 52 weeks' duration, epistaxis was observed more frequently in patients 38 treated with Dymista Nasal Spray than those who received placebo [*see Adverse Reactions (6)*].

Instances of nasal ulceration and nasal septal perforation have been reported in patients following the intranasal application of corticosteroids. There were no instances of nasal ulceration or nasal septal perforation observed in clinical trials with Dymista Nasal Spray. Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal ulcers, nasal surgery, or nasal trauma should not use Dymista Nasal Spray until healing has occurred. In clinical trials with fluticasone propionate administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred. When such an infection develops, it may require treatment with appropriate local therapy and discontinuation of treatment with Dymista Nasal Spray. Patients using Dymista Nasal Spray over several months or longer should be examined periodically for evidence of *Candida* infection or other signs of adverse effects on the nasal mucosa.

5.3 Glaucoma and Cataracts

Nasal and inhaled corticosteroids may result in the development of glaucoma and/or cataracts. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

Glaucoma and cataract formation were evaluated with intraocular pressure measurements and slit 56 lamp examinations in a controlled 12-month study in 612 adolescent and adult patients aged 12 years and older with perennial allergic or vasomotor rhinitis (VMR). Of the 612 patients enrolled in the study, 405 were randomized to receive Dymista Nasal Spray (1 spray per nostril twice daily) and 207 were randomized to receive fluticasone propionate nasal spray (2 sprays per nostril once daily). In the Dymista Nasal Spray group, one patient had increased intraocular pressure at month 6. In addition, three patients had evidence of posterior subcapsular cataract at month 6 and one at month 12 (end of treatment). In the fluticasone propionate group, three patients had evidence of posterior subcapsular cataract at month 12 (end of treatment).

5.4 Immunosuppression

Persons who are using drugs, such as corticosteroids, that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin 74 (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

Corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract; untreated local or systemic fungal or bacterial infections; systemic viral or parasitic infections; or ocular herpes simplex because of the potential for worsening of these infections.

5.5 Hypothalamic-Pituitary-Adrenal (HPA) Axis Effects

When intranasal steroids are used at higher than recommended dosages or in susceptible individuals at recommended dosages, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, the dosage of Dymista Nasal Spray should be discontinued slowly, consistent with accepted procedures for discontinuing oral corticosteroid therapy. The concomitant use of intranasal corticosteroids with other inhaled corticosteroids could increase the risk of signs or symptoms of hypercorticism and/or suppression of the HPA axis. The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency, and in addition some patients may experience symptoms of withdrawal, e.g., joint and/or muscular pain, lassitude, and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticosteroids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

5.6 Use of Cytochrome P450 3A4 Inhibitors

Ritonavir and other strong cytochrome P450 3A4 (CYP3A4) inhibitors can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations [*see Drug Interactions (7.2) and Clinical Pharmacology (12.3)*]. During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of Dymista Nasal Spray and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

Use caution with the coadministration of Dymista Nasal Spray and other potent CYP3A4 inhibitors, such as ketoconazole [*see Drug Interactions (7.2) and Clinical Pharmacology (12.3)*].

5.7 Effect on Growth

Corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth routinely of pediatric patients receiving Dymista Nasal Spray [*see Use in Specific Populations (8.4)*].

6 ADVERSE REACTIONS

Systemic and local corticosteroid use may result in the following:

- Somnolence [*see Warnings and Precautions (5.1)*]
- Local nasal effects, including epistaxis, nasal ulceration, nasal septal perforation, impaired wound healing, and *Candida albicans* infection [*see Warnings and Precautions (5.2)*]
- Cataracts and glaucoma [*see Warnings and Precautions (5.3)*]
- Immunosuppression [*see Warnings and Precautions (5.4)*]
- Hypothalamic-pituitary-adrenal (HPA) axis effects, including growth reduction [*see Warnings and Precautions (5.5 and 5.7), Use in Specific Populations (8.4)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect rates observed in practice. The safety data described below reflect exposure to Dymista Nasal Spray in 853 patients (12 years of age and older; 36% male and 64% female) with seasonal allergic rhinitis in 3 doubleblind, placebo-controlled clinical trials of 2-week duration. The racial distribution for the 3 clinical trials was 80% white, 16% black, 2% Asian, and 1% other. In the 12-month open-label, active-controlled clinical trial, 404 Asian patients (240 males and 164 females) with perennial allergic rhinitis or vasomotor rhinitis were treated with Dymista Nasal Spray, 1 spray per nostril twice daily.

Adults and Adolescents 12 Years of Age and Older

In the 3 placebo-controlled clinical trials of 2-week duration, 3411 patients with seasonal allergic rhinitis were treated with 1 spray per nostril of Dymista Nasal Spray, azelastine hydrochloride nasal spray, fluticasone propionate nasal spray, or placebo, twice daily. The azelastine hydrochloride and fluticasone propionate comparators use the same vehicle and device as Dymista Nasal Spray and are not commercially marketed. Overall, adverse reactions were 16% in the Dymista Nasal Spray treatment groups, 15% in the azelastine hydrochloride nasal spray groups, 13% in the fluticasone propionate nasal spray groups, and 12% in the placebo groups. Overall, 1% of patients in both the Dymista Nasal Spray and placebo groups discontinued due to adverse reactions.

Table 1 contains adverse reactions reported with frequencies greater than or equal to 2% and more frequently than placebo in patients treated with Dymista Nasal Spray in the seasonal allergic rhinitis controlled clinical trials.

Table 1. Adverse Reactions with ≥2% Incidence and More Frequently than Placebo in Placebo-Controlled Trials of 2 Weeks Duration with Dymista Nasal Spray in Adult and Adolescent Patients With Seasonal Allergic Rhinitis

	1 spray per nostril twice daily			
	Dymista Nasal Spray (N=853)*	Azelastine Hydrochloride Nasal Spray† (N=851)	Fluticasone Propionate Nasal Spray† (N=846)	Vehicle Placebo (N=861)
Dysgeusia	30 (4%)	44 (5%)	4 (1%)	2 (<1%)
Headache	18 (2%)	20 (2%)	20 (2%)	10 (1%)
Epistaxis	16 (2%)	14 (2%)	14 (2%)	15 (2%)

*Safety population N=853, intent-to-treat population N=848

†Not commercially marketed

In the above trials, somnolence was reported in <1% of patients treated with Dymista Nasal Spray (6 of 853) or vehicle placebo (1 of 861) [*see Warnings and Precautions (5.1)*].

Long-Term (12-Month) Safety Trial:

In the 12-month, open-label, active-controlled, long-term safety trial, 404 patients (12 years of age and older) with perennial allergic rhinitis or vasomotor rhinitis were treated with Dymista Nasal Spray 1 spray per nostril twice daily and 207 patients were treated with fluticasone propionate nasal spray, 2 sprays per nostril once daily. Overall, adverse reactions were 47% in the Dymista Nasal Spray treatment group and 44% in the fluticasone propionate nasal spray group. The most frequently reported adverse reactions (≥ 2%) with Dymista Nasal Spray were headache, pyrexia, cough, nasal congestion, rhinitis, dysgeusia, viral infection, upper respiratory tract infection, pharyngitis, pain, diarrhea, and epistaxis. In the Dymista Nasal Spray treatment

group, 7 patients (2%) had mild epistaxis and 1 patient (<1%) had moderate epistaxis. In the fluticasone propionate nasal spray treatment group 1 patient (<1%) had mild epistaxis. No patients had reports of severe epistaxis. Focused nasal examinations were performed and no nasal ulcerations or septal perforations were observed. Eleven of 404 patients (3%) treated with Dymista Nasal Spray and 6 of 207 patients (3%) treated with fluticasone propionate nasal spray discontinued from the trial due to adverse events.

7 DRUG INTERACTIONS

No formal drug interaction studies have been performed with Dymista Nasal Spray. The drug interactions of the combination are expected to reflect those of the individual components.

7.1 Central Nervous System Depressants

Concurrent use of Dymista Nasal Spray with alcohol or other central nervous system depressants should be avoided because somnolence and impairment of central nervous system performance may occur [*see Warnings and Precautions (5.1)*].

7.2 Cytochrome P450 3A4

Ritonavir (a strong CYP3A4 inhibitor) significantly increased plasma fluticasone propionate exposure following administration of fluticasone propionate aqueous nasal spray, resulting in significantly reduced serum cortisol concentrations [*see Clinical Pharmacology (12.3)*]. During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

Ketoconazole (also a strong CYP3A4 inhibitor), administered in multiple 200 mg doses to steady-state, increased plasma exposure of fluticasone propionate, reduced plasma cortisol AUC, but had no effect on urinary excretion of cortisol, following administration of a single 1000 mcg dose of fluticasone propionate by oral inhalation route.

Caution should be exercised when Dymista Nasal Spray is coadministered with ketoconazole and other known strong CYP3A4 inhibitors.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Dymista Nasal Spray: Teratogenic Effects: Pregnancy Category C:

There are no adequate and well-controlled clinical trials of Dymista Nasal Spray, azelastine hydrochloride only, or fluticasone propionate only in pregnant women. Animal reproductive studies of azelastine hydrochloride and fluticasone propionate in mice, rats, and/or rabbits revealed evidence of teratogenicity as well as other developmental toxic effects. Because animal reproduction studies are not always predictive of human response, Dymista Nasal Spray should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Azelastine hydrochloride: Teratogenic Effects: In mice, azelastine hydrochloride caused embryo-fetal death, malformations (cleft palate; short or absent tail; fused, absent or branched ribs), delayed ossification, and decreased fetal weight at an oral dose approximately 610 times the maximum recommended human daily intranasal dose (MRHDID) in adults (on a mg/m2 basis at a maternal dose of 68.6 mg/kg). This dose also caused maternal toxicity as evidenced by decreased body weight. Neither fetal nor maternal effects occurred at a dose that was approximately 26 times the MRHDID (on a mg/m2 basis at a maternal dose of 3 mg/kg).

In rats, azelastine hydrochloride caused malformations (oligo- and brachydactylia), delayed ossification and skeletal variations, in the absence of maternal toxicity, at an oral dose approximately 530 times the MRHDID in adults (on a mg/m2 basis at a maternal dose of 30 mg/kg). At a dose approximately 1200 times the MRHDID (on a mg/m2 basis at a maternal dose of 68.6 mg/kg), azelastine hydrochloride also caused embryo-fetal death and decreased fetal weight; however, this dose caused severe maternal toxicity. Neither fetal nor maternal effects occurred at a dose approximately 53 times the MRHDID (on a mg/m2 basis at a maternal dose of 3 mg/kg).

In rabbits, azelastine hydrochloride caused abortion, delayed ossification, and decreased fetal weight at oral doses approximately 1100 times the MRHDID in adults (on a mg/m2 basis at a maternal dose of 30 mg/kg); however, these doses also resulted in severe maternal toxicity. Neither fetal nor maternal effects occurred at a dose approximately 11 times the MRHDID (on a mg/m2 basis at a maternal dose of 0.3 mg/kg).

Fluticasone propionate: Teratogenic Effects: Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Subcutaneous studies in the mouse and rat at doses approximately equivalent to and 4 times, respectively, the MRHDID in adults (on a mcg/m2 basis at maternal doses of 45 and 100 mcg/kg respectively), revealed fetal toxicity characteristic of potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification.

In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose less than the MRHDID in adults (on a mcg/m2 basis at a maternal dose of 4 mcg/kg). However, no teratogenic effects were reported at oral doses up to approximately 25 times the MRHDID in adults (on a mcg/m2 basis at a maternal dose of 300 mcg/kg) of fluticasone propionate to the rabbit. No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration [*see Clinical Pharmacology (12.3)*].

Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Nonteratogenic Effects: Fluticasone propionate crossed the placenta following oral administration of approximately 4 and 25 times the MRHDID in adults (on a mcg/m2 basis at maternal doses of 100 mcg/kg and 300 mcg/kg to rats and rabbits, respectively).

8.3 Nursing Mothers

Dymista Nasal Spray: It is not known whether Dymista Nasal Spray is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when Dymista Nasal Spray is administered to a nursing woman. Since there are no data from well-controlled human studies on the use of Dymista Nasal Spray by nursing mothers, based on data from the individual components, a decision should be made whether to discontinue nursing or to discontinue Dymista Nasal Spray, taking into account the importance of Dymista Nasal Spray to the mother.

Azelastine hydrochloride: It is not known if azelastine hydrochloride is excreted in human milk.

Fluticasone propionate: It is not known if fluticasone propionate is excreted in human milk. However, other corticosteroids are excreted in human milk. Subcutaneous administration to lactating rats of 10 mcg/kg of tritiated fluticasone propionate (less than the maximum recommended daily intranasal dose in adults on a mcg/m2 basis) resulted in measurable radioactivity in the milk.

8.4 Pediatric Use

Safety and effectiveness of Dymista Nasal Spray in pediatric patients below the age of 12 years have not been established.

Controlled clinical studies have shown that intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for "catch-up" growth following discontinuation of treatment with intranasal corticosteroids has not been adequately studied. The growth of pediatric patients receiving intranasal corticosteroids, including Dymista Nasal Spray, should be monitored routinely (e.g., via stadiometry). The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained and the risks/benefits of treatment alternatives.

8.5 Geriatric Use

Clinical trials of Dymista Nasal Spray did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

10 OVERDOSAGE

Dymista Nasal Spray: Dymista Nasal Spray contains both azelastine hydrochloride and fluticasone propionate; therefore, the risks associated with overdosage for the individual components described below apply to Dymista Nasal Spray.

Azelastine hydrochloride: There have been no reported overdosages with azelastine hydrochloride. Acute azelastine hydrochloride overdosage by adults with this dosage form is unlikely to result in clinically significant adverse events, other than increased somnolence, since one (1) 23 g bottle of Dymista Nasal Spray contains approximately 23 mg of azelastine hydrochloride. Clinical trials in adults with single doses of the oral formulation of azelastine hydrochloride (up to 16 mg) have not resulted in increased incidence of serious adverse events. General supportive measures should be employed if overdosage occurs. There is no known antidote to Dymista Nasal Spray. Oral ingestion of antihistamines has the potential to cause serious adverse effects in children. Accordingly, Dymista Nasal Spray should be kept out of the reach of children.

Fluticasone propionate: Chronic fluticasone propionate overdosage may result in signs/symptoms of hypercorticism [*see Warnings and Precautions (5.2)*]. Intranasal administration of 2 mg (10 times the recommended dose) of fluticasone propionate twice daily for 7 days to healthy human volunteers was well tolerated. Single oral fluticasone propionate doses up to 16 mg have been studied in human volunteers with no acute toxic effects reported. Repeat oral doses up to 80 mg daily for 10 days in volunteers and repeat oral doses up to 10 mg daily for 14 days in patients were well tolerated. Adverse reactions were of mild or moderate severity, and incidences were similar in active and placebo treatment groups. Acute overdosage with this dosage form is unlikely since one (1) 23 g bottle of Dymista Nasal Spray contains approximately 8.5 mg of fluticasone propionate.

DYMISTA™
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Interoperability Issues Limit EHR Data Sharing

Physicians are willing, but technology and costs stymie progress, survey suggests.

BY MARY ELLEN SCHNEIDER
IMNG Medical News

Technical barriers and costs are holding back electronic sharing of clinical data, according to the results of a recent survey conducted by a consortium of physician associations.

More than 70% of the physicians polled said that their electronic health record (EHR) system was unable to communicate electronically with other systems – a lack of interoperability that prevents electronic exchange of information. Another barrier is the cost of setting up and maintaining interfaces and exchanges to share information.

The survey findings are not surprising, Dr. Michael Barr, senior vice president in the division of medical practice, professionalism, and quality at the American College of Physicians, said during a forum sponsored by the Bipartisan Policy Center in Washington. They do, however, highlight the progress that physicians have made in embracing EHRs.

Several years ago, this type of survey might have shown that physicians wanted to keep the status quo or that they feared change, he said. Now, the barriers to exchanging information have more to do with technology than physician attitudes.

Making progress on interoperability will be essential as physicians move forward with different care delivery models such as the patient-centered medical home and the medical home neighborhood, which includes subspecialists, Dr. Barr said.

"The success of these new models will depend on health IT infrastructure that supports seamless coordination of care, patient engagement, and clinical information exchange," he said.

"You can't do team-based care unless everybody has access to the information appropriately."

Beyond interoperability, there are still challenges for physicians seeking to implement EHRs in their practices, said Dr. Robert M. Wah, immediate past chair of the board of trustees of the American Medical Association.

'You can't do team-based care unless everybody has access to the information appropriately.'

DR. BARR

The money available through the Medicare and Medicaid Electronic Health Record Incentive Programs is beginning to change that equation, he said, but most physicians still say that the incentives offered aren't sufficient to offset the loss in productivity, the change in their workflow, and the assorted other expenses of bringing on EHRs. "We're still very concerned about that as a barrier," Dr. Wah said.

The physician survey was developed by the American College of Physicians and Doctors Helping Doctors Transform Health Care. The American College of Surgeons, the Association of Medical Directors of Information Systems, and the American Academy of Pediatrics also were involved with the survey. The groups circulated the survey to thousands of their members and received responses from more than 500 physicians.

About three-quarters of the respondents were using an EHR at the time of the survey, higher than the national average of about 55%, according to the National Center for Health Statistics. As a result, the survey developers cautioned that the results should not be used to reflect the view of U.S. physicians as a whole.

The respondents were mostly from

Continued on following page

Unit-Based Patient Safety Program Gets a Tool Kit

Approach has been used successfully to fight central line–associated bloodstream infections.

BY SHARON WORCESTER
IMNG Medical News

The Agency for Healthcare Research and Quality's Comprehensive Unit-Based Safety Program has proved effective for helping clinical teams tackle tough patient safety issues, and now the agency has introduced a tool kit to assist with implementation of the program nationwide.

People feel comfortable learning as a team from each preventable infection.

DR. PATTERSON

The Comprehensive Unit-Based Safety Program, or CUSP, is a science-based change package initially conceived by Dr. Peter J. Pronovost of Johns Hopkins University, Baltimore, to help prevent potentially deadly central line–associated bloodstream infections (CLABSIs) in hospital intensive care units, but with the help of the new tool kit developed with funding from the AHRQ, the program can be applied to any safety problem at the unit level. Numerous studies have demonstrated the effectiveness of the program for lowering infection rates, and preliminary results from a national study confirm those findings.

Implementation of CUSP at more than 1,100 adult intensive care units in 44 states over a 4-year period reduced the rate of CLABSIs by 40%, Dr. Carolyn M. Clancy, director of AHRQ, reported during a press conference held in conjunction with the AHRQ annual conference.

"That's not just a number," she said, stressing that the 40% reduction equates to 500 lives saved, 2,000 CLABSIs prevented, and $34 million in health care costs avoided. Some hospitals were able to achieve even better results, reducing the rate of CLABSIs to zero, she said.

One such hospital is Peterson Regional Medical Center in Kerrville, Tex., which has had zero CLABSIs in the entire hospital for more than 30 months since implementing CUSP.

"In my 32 years as a nurse, the CUSP program is the most powerful program I have ever seen," said Theresa Hickman, a nurse educator and the team leader for the 124-bed hospital's participation in the national initiative.

Historically, those on the front lines in health care – such as nurses – have not been included in safety programs, but CUSP turns that model on its head, empowering frontline caregivers to make a difference, she said.

Indeed, CUSP combines clinical best practices with an understanding of the science of safety and improved patient safety culture to empower hospital teams to address identified safety issues, Dr. Clancy said.

The Society for Healthcare Epidemiology of America agreed. Within CUSP, "members of the health care team feel comfortable speaking up and learning as a team the lessons learned of each preventable infection. This demonstrated success shows culture change is possible by involving every member of the health care team in an effort that combines science with implementation," Dr. Jan Patterson, SHEA president, said in a statement. Dr. Patterson is director of the Center for Patient Safety and Health Policy at the University of Texas Health Science Center in San Antonio.

The tool kit, which is available at www.ahrq.gov/cusptoolkit, is a multipronged quality improvement program developed by clinicians for clinicians. It is "modular, customizable, and self-paced," she said, noting that the package includes step-by-step instructor guides, presentation materials, implementation tools, and instructional videos, all of which can be used to address any patient safety issue.

Some of the hospitals that have successfully used the CUSP tool kit to reduce CLABSIs are now using it to fight other types of infections as well, such as urinary tract infections and ventilator-associated pneumonia, she said, noting that the tool kit can be modified to meet the unique needs of a specific unit, and that the concept of CUSP can be implemented facility-wide.

An important lesson from the dramatic results seen with CUSP is that health care–related infections should not be seen as an unfortunate but inevitable consequence of care.

"No one should become sicker due to the care they receive," Dr. Patterson said, adding that results of the study have changed the idea of what is possible.

Rich Umbdenstock, president and chief executive officer of the American Hospital Association, which collaborated with AHRQ on promoting and implementing CUSP, agreed, saying that "by working together, we can achieve these positive results on a national level."

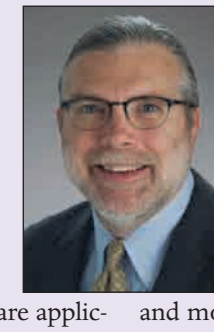
Already, hospitals are seeing infection rates previously believed impossible, Dr. Pronovost said: "That "this could be health care's 'man on the moon' moment."

"With these results, health care is taking a giant step forward. … This program offers hope for us about what's possible when policy makers invest in the science of safety," he said.

The speakers reported having no relevant conflicts of interest. ■

COMMENTARY

Dr. Steven Q. Simpson, FCCP, comments: CUSP, the Comprehensive Unit-based Safety Program, has a proven track record for reducing and even eliminating hospital-acquired infections. However, there is no reason to believe that the methodology's benefits should be limited to infection; the techniques are applicable to many clinical situations within the ICU and the hospital, at large. The ACCP has already taken a leadership role by its contributions to HHS's awards for leadership and sustained excellence in reducing ICU-acquired infections. As College members, we should take advantage of AHRQ's CUSP education program to broaden our safety net, to make our ICUs safer and more efficient, and to enhance our patients' chances of returning home to the people they love and the activities that make them happy.



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small practices. Nearly three-quarters of the physicians surveyed worked in practices with 10 or fewer physicians and more than half were in practices of 5 or fewer physicians.

Physicians still say incentives aren't enough to offset productivity losses and related expenses.

DR. WAH

The survey also provides a more detailed picture of the type of EHR functionality that physicians say would help them better manage care transitions, such as when they refer a patient, when a patient is discharged from the hospital, and when a patient is referred by another physician. More than 80% of those surveyed said that medication lists, relevant laboratory test results, and results from relevant imaging tests were "very important" or "essential."

Physicians indicated that they wanted to have this type of essential patient data pushed to them, possibly though secure e-mail. They also wanted the ability to look up additional patient information in the electronic record.

The survey results could be helpful in accelerating the move toward interoperability in EHRs.

A companion report from the Bipartisan Policy Center recommended that clinicians from across specialties and care settings develop a consensus on what types of clinical information should be shared, how they want to receive it, and reasonable timeframes for delivering the data. That consensus information could be used, along with technical standards, to help craft a national strategy for health IT interoperability, according to the report. ■

ICD-10 Bell Won't Toll Till 2014

BY ALICIA AULT
IMNG Medical News

Implementation of the diagnosis and procedure codes in the 10th edition of the International Classification of Diseases has been put off for another year, according to the Centers for Medicare and Medicaid Services.

Many hospitals and physicians have expressed deep concern that they would not be able to meet the Oct. 1, 2013, deadline for using ICD-10. In April, the federal agency said in a proposed rule that it would delay compliance by a year; the final decision was announced in a rule that primarily establishes a standard unique identifier for health plans to help smooth payment transactions for hospitals and physicians.

"We believe the change in the compliance date for ICD-10 gives covered health care providers and other covered entities more time to prepare and fully test their systems to ensure a smooth and coordinated transition by all covered entities," CMS officials wrote in a statement.

"A smooth transition to the updated medical data code sets" is essential, they emphasized, "as the failure of any one industry segment to achieve compliance would negatively affect all other industry segments and result in returned claims and provider payment delays." ■

ACCP Fellow Appointed to Chair AMA RUC Committee

BY TRICIA BARDON

ACCP MANAGER, CODING AND REIMBURSEMENT

Congratulations to Dr. Scott Manaker, PhD, FCCP, on his recent appointment to the prestigious, highly visible position as Chair of the American Medical Association's (AMA) Relative Value Update Committee (RUC) for the Practice Expense Advisory Committee (PEAC). Dr. Manaker began serving as the ACCP's RUC Advisor in 1996. He has worked tirelessly on behalf of the ACCP membership for the past 15 years. His stellar knowledge of payment policy, clinical documentation, and participation as the ACCP RUC Advisor led to his election in serving the Pulmonary/Critical Care/Sleep for two separate terms in a rotating internal medicine seat on the RUC.

The PEAC subcommittee is vital to you and every provider in the nation. This body recommends, to the RUC, the values for practice expense (PE) for each and every one of the 8,600 CPT® codes, many of which you use in your practice. Approximately 48% of each payment you receive, if it is valued on the Medicare Physician Fee Schedule (MPFS), is for the expenses in your office. Often times, this job is very detailed and time consuming and is carried out during the triennial meetings of the RUC. The Chair position will take much of Dr. Manaker's time working for the physician community and each ACCP member.

Practice expense relative values were initially based on a formula using average Medicare-approved charges from 1991, which was the year the relative-based values system (RBRVS) was implemented. In 1999, the Centers for Medicare and Medicaid Services (CMS) moved to a resource-based relative value for each CPT code that will be different depending on the site of service.

Most recently, CMS decided to use a survey from physician specialties, like ACCP, to better determine the PE. This survey was the Physician Practice Information Survey (PPIS), in which ACCP participated, to identify the expenses in a more

Continued on following page

COMMENTARY

Dr. Alan Plummer, FCCP, comments about the appointment of Dr. Manaker: "I think the appointment of Scott as Chairman of the PE Subcommittee is a tribute to his knowledge and many contributions to the RUC since he has been involved with the RUC.

I was very pleased with his well-deserved appointment. I believe he started working with the RUC as a member of the PEAC (Practice Expense Advisory Committee), which was a forerunner of the PERC (Practice Expense Review Committee), which is now the PE (Practice Expense) Subcommittee.

The majority of the payment for each CPT code is from the practice expense component. That is why the actions of the PE Subcommittee are so important.

I think Scott is an excellent choice and don't believe they could have found a better individual to Chair the Subcommittee. He is a very visible, credible member of the chest community involved with the activities of the RUC. He has just rotated off the RUC Committee as the Rotating Medicine member, which was his second rotation in this position. He represents the pulmonary community very well at the RUC and lifts the stature of the RUC efforts by the ACCP and the ATS Advisors and Alternate Advisors."

Continued from previous page

realistic and granular way.

The AMA actively monitors and adjusts all phases in the refinement of PE relative values. It is imperative that CMS has the correct information for actual PE data. CMS relies heavily on the PE subcommittee and its methodology to determine the value you receive for this part of the fee schedule. The CMS acceptance for the PE values has an enormous impact on all of your payments. Many third-party payers follow CMS recommendations, so you most likely are reimbursed most often based on this methodology for your practice expenses.

The PE subcommittee values the labor activities, medical supplies used, and any equipment you may use in your practice. This activity is especially important for procedural positions, as you use more equipment and clinical staff time for these codes.

After the PEAC deliberates and approves the values for a code (either a new or established code), the issue is then sent to the full RUC panel for approval, and the final recommendation is established. This recommended value is then sent to CMS for their approval and acceptance. If approved, the value is established in the final rule that is published once a year in November to begin the new payment schedule of January 1st of the upcoming calendar year. ACCP staff closely monitors this rule and will have the information for members on its website for your use in your practice. This information can also help you to make decisions on how you may use your staff time, supplies, and, sometimes, the decision to purchase new equipment. The PEAC uses specialty societies to make recommendations for new or revised CPT codes just as the RUC panel does.

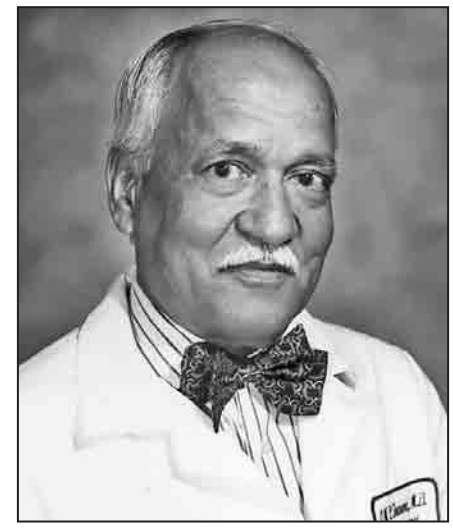
Over the years since the PE subcommittee was established, it has made recommendations to more than 6,500 medical procedures. The composition of the PEAC mirrors the composition of the RUC body and also has representation from the nurse community. Medical specialty societies recommend and nominate representatives to the panel relying on the specialties to recommend experts for the society when a seat opens. The Chair and Vice-Chair positions are appointed by the RUC Chair, Barbary Levy, M.D.

We congratulate and thank Dr. Manaker and hope you will do the same when you see him at CHEST 2012 or at any other occasion. ■

In Remembrance: Dr. Om Sharma, Master FCCP

Dr. Om Sharma, M.D., Master FCCP, died on August 19, 2012, in Los Angeles, California.

He was world-recognized for his expertise in sarcoidosis and made significant contributions in the field of interstitial lung diseases. A lifelong teacher and mentor and a prolific author, Dr. Sharma lectured around the world. He was one of the founders of World Association of Sarcoidosis and Other Granulomatous Disorders and was its president for many years. His work on clinical aspects of the disease spanned more than 40 years. Dr. Sharma was honored as a Master FCCP in 2006. He served the ACCP in many capacities, including Chair of the Membership Committee and Chair of the Council of Governors and held positions also with The CHEST Foundation.



DR. OM SHARMA, MASTER FCCP

ACCP President, Dr. Suhail Raoof, FCCP, remembered Dr. Sharma with these words: "He led by example, putting in perspective the qualities that really matter in life. He doctored his patients; he rejoiced in alleviating and mitigating their sufferings. He mentored his trainees and acquaintances and genuinely rejoiced in seeing them advancing in their careers and doing well in life. Like thousands of other friends, students, and colleagues, I feel privileged and honored to have known him and to have observed him closely. Today, and for a very long time, he will be remembered by those whose lives he touched." ■

NETWORKS
Pediatric Chest Medicine, PFT Labs, Lung Cancer Initiatives

Pediatric Chest Medicine

Medicaid to Reimburse at 2012 Medicare Levels

Pediatric pulmonologists and intensivists will be paid 2012 Medicare rates for many services they provide in calendar years 2013 and 2014, according to the proposed rule issued this summer by the Centers for Medicare and Medicaid Services (CMS). The final rule will be issued sometime in late October.

Medicaid is a federally mandated program for the aged, blind, and disabled, as well as children living in poverty. Each state manages and partially funds its own Medicaid program with federal matching grants. The State Children's Health Insurance Program (SCHIP) provides funding for additional children near the poverty level, with eligibility varying from state to state. Both programs would be affected by the proposed rule from CMS.

Not all codes will get the increased reimbursement. Codes included in the proposed rule encompass most of the evaluation and management (E/M) codes, critical care codes, and NICU codes. Not included in the proposed rule are most of the procedural codes, such as bronchoscopy, pulmonary function testing, radiology, and unbundled critical care procedures.

Medicaid payment rates are nearly universally lower than Medicare rates, at present. In New Jersey, Medicaid rates are 37% of those paid for Medicare. In Georgia, Medicaid or the SCHIP program insures approximately half of the pediatric population of the state. It currently reimburses at approximately 69% of Medicare levels. The proposed change in payment policy should positively impact pediatric subspecialists across the nation. The ACCP supported this portion of the proposed rule during the comment period, advocating publicly for its pediatric members. Of note, the proposed rule bases reimbursement on 2012 Medicare rates and would not be subject to reductions in the 2013 Medicare provider reimbursement rates that may come about from reductions mandated by the sustained growth rate (SGR) provisions.

Dr. Burt Lesnick, FCCP
Chair

Pulmonary Physiology, Function, and Rehabilitation

PFT Labs

Over the last year, the Pulmonary Physiology, Function, and Rehabilitation NetWork has shown continued growth in the scope and contribution of the NetWork. There continues to be active participation from the steering committee, and we have welcomed three new members this year.

General issues in our NetWork continue to revolve around the management of pulmonary function testing labs. This includes analysis of predicted values, responsibilities of medical directors, use and standardization of 6-minute walk tests, and coordination of patient data with EMR systems. We also continue to work on improving our profile in the e-Community initiatives.

We will have an informative profile at CHEST 2012 that includes educational lecture and poster sessions, participation in a NetWork open house, and a NetWork forum led by a pulmonary hypertension expert who will review the role of pulmonary rehabilitation in pulmonary hypertension. Other CHEST sessions include a comprehensive review of preoperative respiratory and sleep evaluation and postoperative care in pulmonary patients.

I would like to conclude by thanking the committee in general for their efforts and by recognizing Dr. F. Sciurba for his leadership over the last 2 years.

Dr. Jeffrey Cary, FCCP
Vice-Chair

Thoracic Oncology NetWork

Lung Cancer Initiatives

The Thoracic Oncology NetWork has been very active in keeping up with the rapidly evolving world of thoracic cancers.

Members of the NetWork and the steering committee have been focusing on projects that include how to identify, measure, and, ultimately, improve quality in the care of patients with lung cancer. The ultimate goal of this evolving project is to reduce variations in practice, which can (by definition) lead to suboptimal care of this complex group of patients.

Other projects emerging from the NetWork include the upcoming 3rd edition of the Evidence-Based Guidelines for the Diagnosis and Treatment of Lung Cancer. This multiyear project aims to provide a basis of evidence and use an iterative process to review the evidence and make sound recommendations for everything from the solitary pulmonary nodule to the provision of palliative care of patients at the end of life.

This project will be submitted to *CHEST* in 2013 and should be available after publication as an online resource to all practitioners.

Members have been increasingly active on the ACCP e-Community portal. A recent discussion revolved around the use of segmentectomy vs stereotactic body radiotherapy (SBRT) for patients with poor pulmonary function.

Participants described the multidisciplinary approaches of their own institutions, as well as discussed the recent cogent clinical studies. Other discussion topics have been diverse and provocative.

We invite all individuals interested in thoracic oncology to join the discussion.

Dr. David Tom Cooke FCCP
Steering Committee Member

This Month in *CHEST*: Editor's Picks

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

► Clinical and Biologic Features of Patients Suspected or Confirmed to Have Heparin-Induced Thrombocytopenia in a Cardiothoracic Surgical ICU. By Dr. V. Trehel-Tursis et al.

► Independent Association of Urinary F_2 - Isoprostanes With Survival in Pulmonary Arterial Hypertension. By Dr. J-L Cracowski et al.

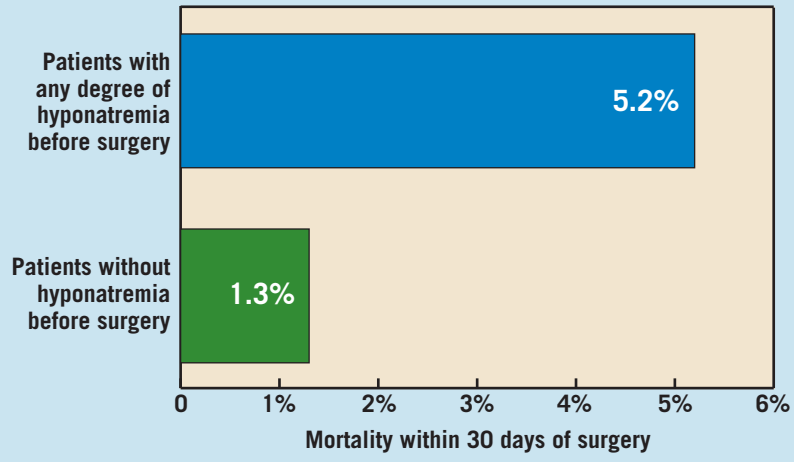
► The Complex Relationship of Serum Adiponectin to COPD Outcomes. By Dr. H. I. Yoon et al.

► Transvenous Phrenic Nerve Stimulation in Patients With Cheyne-Stokes Respiration and Congestive Heart Failure: A Safety and Proof-of-Concept Study. By Dr. X-L Zhang et al.

► Exercise Pathophysiology in Patients With Chronic Mountain Sickness. By Dr. H. Groepenhoff et al.

DATA WATCH

Hyponatremia Linked to Postsurgical Mortality



Note: Based on an observational study of 964,263 adults undergoing major surgery.
Source: Arch. Intern. Med. Sept. 10, 2012 (doi:10.1001/archinternmed.2012.3992)

IMNG Medical Media

For PAH (WHO Group 1) patients on oral monotherapy

TYVASO: the ONLY inhaled prostacyclin analogue approved for 4x-daily dosing[1]

Short treatment sessions: just 2 to 3 minutes each[2]

ONLY inhaled prostacyclin analogue approved as an add-on to oral PAH monotherapy[1]

- 52% of patients improved 6MWD by greater than 20 m[3]
- Improvement in 6MWD at peak (20 m) and trough (14 m) exposure[3]

Dosing regimen fits into patients' schedules

- Short treatment sessions: just 2 to 3 minutes, 4x daily[2]
- Set up once daily[1,2]
  - —One plastic ampule per day—no need to replace ampule for each treatment session[1]
  - —About 5 minutes a day for device preparation—once in the morning, and the device is ready to go all day[2]
- Treatment timing can be adjusted for planned activities[1]

Adverse events

- The most common adverse events seen with Tyvaso in ≥4% of PAH patients and more than 3% greater than placebo in the placebo-controlled clinical study were cough, headache, throat irritation/pharyngolaryngeal pain, nausea, flushing, and syncope[1]

STUDY DESIGN: TRIUMPH I was a 12-week, randomized, double-blind, placebo-controlled, multicenter study of patients (N=235) with PAH who were receiving a stable dose of bosentan or sildenafil for 3 months before study initiation. Patients were administered either placebo or Tyvaso in 4 daily treatment sessions with a target dose of 9 breaths (54 mcg) per session over the course of the 12-week study. Primary endpoint was change in 6MWD at 12 weeks. Secondary endpoints included time to clinical worsening, Borg dyspnea score, NYHA functional class, trough 6MWD at week 12 (obtained at least 4 hours after study drug administration), peak 6MWD at 6 weeks, quality of life as measured by the MLWHF questionnaire, and PAH signs and symptoms.[3]

INDICATION

Tyvaso is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).

The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities.

While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor). The controlled clinical experience was limited to 12 weeks in duration.

IMPORTANT SAFETY INFORMATION

- Tyvaso is intended for oral inhalation only. Tyvaso is approved for use only with the Tyvaso Inhalation System
- The safety and efficacy of Tyvaso have not been established in patients with significant underlying lung disease (such as asthma or chronic obstructive pulmonary disease) and in patients under 18 years of age. Patients with acute pulmonary infections should be carefully monitored to detect any worsening of lung disease and loss of drug effect
- Tyvaso may increase the risk of bleeding, particularly in patients receiving anticoagulants
- In patients with low systemic arterial pressure, Tyvaso may cause symptomatic hypotension. The concomitant use of Tyvaso with diuretics, antihypertensives, or other vasodilators may increase the risk of symptomatic hypotension
- Hepatic or renal insufficiency may increase exposure to Tyvaso and decrease tolerability. Tyvaso dosage adjustments may be necessary if inhibitors of CYP2C8 such as gemfibrozil or inducers such as rifampin are added or withdrawn
- The most common adverse events seen with Tyvaso in ≥4% of PAH patients and more than 3% greater than placebo in the placebo-controlled clinical study were cough (54% vs 29%), headache (41% vs 23%), throat irritation/pharyngolaryngeal pain (25% vs 14%), nausea (19% vs 11%), flushing (15% vs <1%), and syncope (6% vs <1%)
- Tyvaso should be used in pregnancy only if clearly needed. Caution should be exercised when Tyvaso is administered to nursing women

Please see brief summary of Full Prescribing Information on following page. For more information, please see Full Prescribing Information, Patient Package Insert, and the Tyvaso Inhalation System Instructions for Use manual. These items are available at www.tyvaso.com.

6MWD=6-minute walk distance. MLWHF=Minnesota Living With Heart Failure. NYHA=New York Heart Association. WHO=World Health Organization.

References: 1. Tyvaso [package insert]. Research Triangle Park, NC: United Therapeutics Corporation; 2011. **2.** Tyvaso [patient package insert]. Research Triangle Park, NC: United Therapeutics Corporation; 2011. **3.** McLaughlin VV, Benza RL, Rubin LJ, et al. Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. *J Am Coll Cardiol*. 2010;55(18):1915-1922.

www.tyvaso.com **www.livingpah.com** **1-877-UNITHER**

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To download a QR code reader, visit your smartphone's app store and search for a QR code reader. A number of code reader apps are available.

TYVASO® (treprostinil) INHALATION SOLUTION

PROSTACYCLIN MADE PRACTICAL

United Therapeutics CORPORATION

Critical Care Commentary

Proposed New Ventilator-Associated Event Definition and Process

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the U.S. Centers for Disease Control and Prevention.

Every year, hundreds of thousands of patients in the United States are managed with mechanical ventilatory support, which places them at risk for a variety of complications that are noted to occur in the critically ill patient. One of the most dreaded of these complications is ventilator-associated pneumonia (VAP), which has been surrounded by controversy related to its definition, diagnosis, and its clinical impact. [1-3]

The development of VAP has been reported to increase the cost of care, length of stay, and adversely impact mortality in a group of critically ill patients managed in the ICU.[1] Concern for the possibility of VAP often leads to early and complicated antibiotic regimens that set the stage for the development of additional multidrug-resistant organisms and do not always result in improved patient outcome.[4] In recent years, as hospitals' health-care-associated infection rates have become increasingly tied to reimbursement from the Centers for Medicare and Medicaid Services, position statements and editorials have been published that point out the problems associated with the lack of an objective, reliable surveillance definition for VAP.[5,6] In fact, the ability to exploit the subjectivity of the current VAP definitions would be the only way to achieve a VAP rate of zero, according to Dr. Klompas.[6]

One of the major difficulties with the current definition of VAP is the reliance on chest radiographs to diagnose a new or progressive infiltrate or radiographic change compatible with a pneumonia. Unfortunately, the portable chest radiographs that are obtained on the critically ill, mechanically ventilated patients in the ICU are often complicated by changes in position, volume status, pleural effusions, atelectasis, overlying lines, drains, tubes, etc, which can make it difficult to assess for new or progressive opacities/infiltrates.[5] The current VAP

Continued on following page

Editor's Comments

In this era of changing economics and pay for performance, it was time that a collaborative and diverse group has finally tried to deal with VAP. For years, no agreed upon, clear-cut definition, treatment plan, or diagnostic criteria were in place. As ICU-related complications, catheter-associated urinary tract infections, central line-associated bloodstream infections, and VAP are life-threatening and extremely costly complications, and a clinically accessible definition of VAP will be extremely helpful. I thank the entire working group and our authors for their hard work in a most contentious area. These definitions will certainly have growing pains and eventual changes. But all long journeys start with the first step, and our patients will hopefully be the true beneficiaries as we use less drugs, streamline our practice, and codify state-of-the-art care as possible.

Dr. Peter Spiro, FCCP

Continued from previous page

surveillance definitions require infection preventionists to interpret radiographic reports to determine if there are findings consistent with the criteria outlined in the definitions. The inconsistencies, vagaries, and complicating exposure issues often present great difficulties for infection preventionists in attempting to determine if there was a potential VAP.

In an effort to improve the VAP surveillance definitions, the Centers for Disease Control and Prevention (CDC) convened a working group composed of representatives from the Critical Care Societies Collaborative (the American Association of Critical-Care Nurses, the American College of Chest Physicians, the American Thoracic Society, and the Society of Critical Care Medicine), the American Association for Respiratory Care, the Association of Professionals in Infection Control and Epidemiology, the Council of State and Territorial Epidemiologists, the Healthcare Infection Control Practices Advisory Committee's Surveillance Working Group, the Infectious Diseases Society of America, and the Society for Healthcare Epidemiology of America. The working group strived to create a surveillance definition that would be applied to adults (18 years or older) who are being supported by mechanical ventilation for 3 days or more in acute and long-term acute care hospitals and inpatient rehabilitation facilities. The working group reviewed the current definitions for VAP and concluded that a great deal of the controvery and difficulty in working with the current definitions related to the requirement for a new or progressive radiographic change. The group took the bold step to eliminate the need for a chest radiograph in the identification of ventilator-associated events (VAE—see attached algorithm, overview of the process, and frequently asked questions) and used the requirement for increased FIO_2 and/or PEEP support after a period of 2 days 2 or more of stable or decreaing ventilatory support to identify a patient who was having a ventilator-associated condition (VAC).

Patients who on or after 3 days of mechanical ventilation and within 2 calendar days before or after the onset of worsening oxygenation (with need for sustained, increased Fio_2 and/or PEEP) and who manifest signs of infection (temperature > 100.4° F or < 96.8° F or white blood cell count of 12,000/μL or greater or 4,000/μL or fewer) and have a new antimicobial agent(s) started and continued for 4 or more calendar days are considered to have an infection-related ventilator-associated complication (IVAC). A possible VAP is present when, in addition to the above, there are purulent respiratory secretions from the lungs, bronchi, or trachea that contain 25 or more neutrophils and 10 or fewer squamous cells per low power field or a positive qualitative, quantitative, or semiquantitative culture from sputum, endotracheal aspirate, bronchoalveolar lavage, lung tissue, or protected specimen brush. A probable VAP is present when purulent respiratory secretions are present along with a positive endotracheal aspirate culture with greater than or equal to 10^5 CFU/mL; bronchoalveolar lavage culture greater than or equal to 10^4 CFU/mL; positive lung tissue culture greater than or equal to 10^4 CFU/mL; or positive protected brush culture with greater than or equal to 10^3 CFU/mL. Probable VAP also is present with a positive pleural fluid culture, positive lung histopathologic findings for infection, positive diagnostic test findings for *Legionella* species, or positive diagnostic test findings on respiratory secretions for selected viral pathogens.

The working group sought to develop a definition for VAE that would use objective, clinical data that are available and easy to identify in most mechanically ventilated patients. These data elements are unlikely to be influenced by clinical practice differences among facilities; in addition, it may be possible to capture these data elements electronically. While the new VAE definitions may or may not reflect "true VAP," they will serve as objective measures that will improve the usefulness of surveillance data and, hopefully, inform the development of strategies to prevent complications of mechanical ventilation. More importantly, these definitions are a beginning and will likely undergo refinement as they are applied to clinical settings and comparative data are reviewed and evaluated. The VAP situation is very similar to the controvery surrounding sepsis definitions in the 1980s. Our ability to recognize and manage sepsis was greatly improved once a consensus definition was introduced and then modified as more experience and data were accrued.[7,8]

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Improving Surveillance for Ventilator-Associated Events in Adults

Centers for Disease Control and Prevention (CDC)

Overview and Proposed New Definition Algorithm

What is the National Healthcare Safety Network (NHSN)?

- NHSN is the CDC's healthcare-associated infections (HAI) surveillance system (www.cdc.gov/nhsn). NHSN uses standard methodology and definitions to collect data from U.S. healthcare facilities. More than 5000 healthcare facilities in all 50 states now participate in NHSN. Most participating facilities report data on device-associated HAIs, including ventilator-associated pneumonia (VAP). Many states require hospitals to report HAIs using NHSN.

How is VAP surveillance currently conducted in NHSN?

- NHSN's current pneumonia (PNEU) definitions were last updated in 2002, and were designed to be used for surveillance of all healthcare-associated pneumonia events, including (but not limited to) VAP.
- Three components make up the current PNEU definitions: an "X-Ray" component (required), a "Signs and Symptoms" component (required), and a "Laboratory" component (optional).
- VAP is specifically defined as a PNEU event that occurs at the time a ventilator is in place, or within 48 hours after a ventilator has been in place. There is currently no required duration that the ventilator must be/have been in place for a PNEU to qualify as a VAP.

Why is the CDC changing the way VAP surveillance is done in NHSN?

- The current PNEU definitions are useful for internal quality improvement purposes, but are limited by their subjectivity and complexity. It is necessary to have objective, reliable surveillance definitions for use in public reporting and inter-facility comparisons of event rates and federal pay-for-reporting and -performance programs.

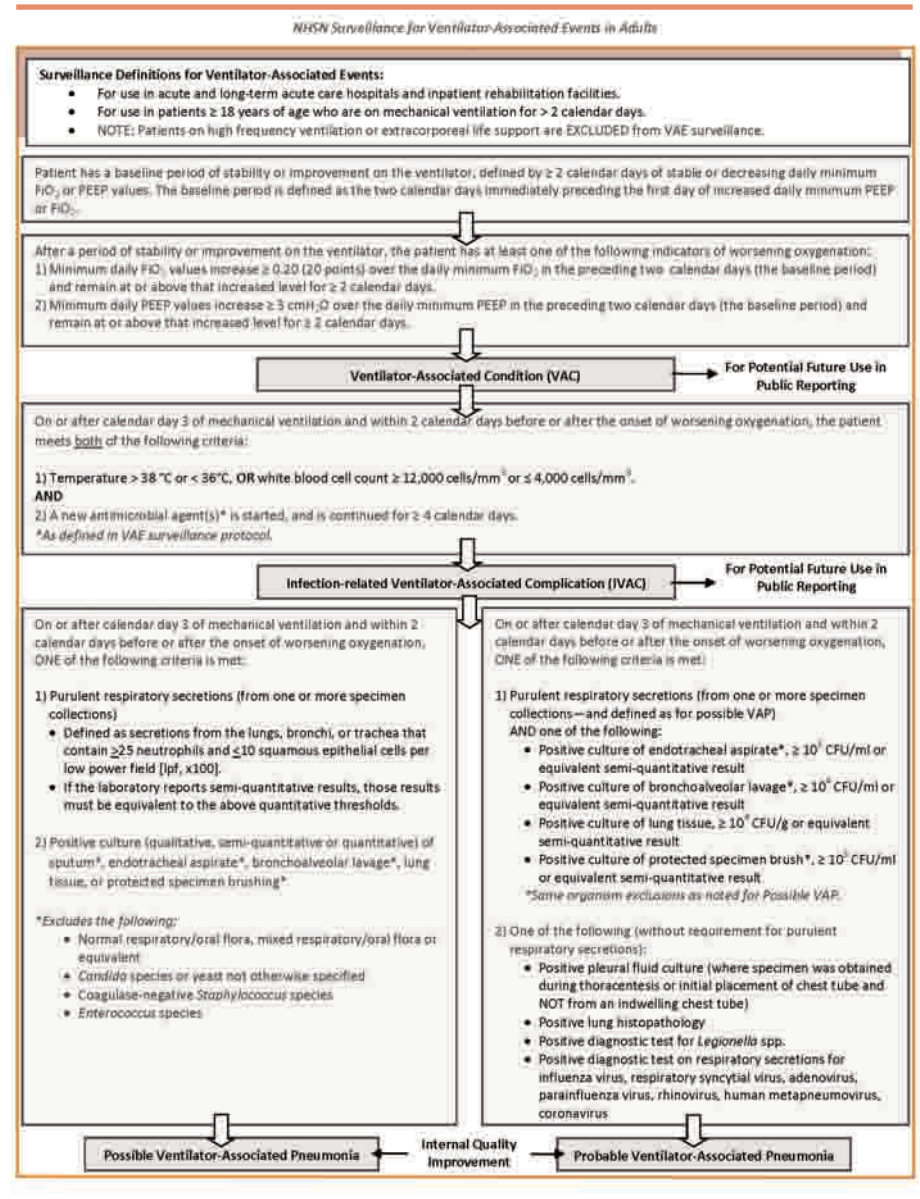
What is the CDC's process for improving NHSN VAP surveillance?

- The CDC's Division of Healthcare Quality Promotion (DHQP) is collaborating with the CDC Prevention Epicenters (http://www.cdc.gov/hai/epicenters), the Critical Care Societies Collaborative (CCSC, http://ccsconline.org), other professional societies and subject matter experts, and federal partners.
- DHQP initiated a collaboration with the CCSC in September 2011, and convened a **VAP Surveillance Definition Working Group**, consisting of representatives from several organizations with expertise in critical care, infectious diseases, healthcare epidemiology and surveillance, and infection control.

Organization	*Representative(s)*
American Association of Critical-Care Nurses	Ms. Suzanne Burns and Ms. Beth Hammer
American Association for Respiratory Care	Dr. Dean Hess
American College of Chest Physicians	Drs. Robert Balk and David Gutterman
American Thoracic Society	Drs. Nicholas Hill and Mitchell Levy
Association of Professionals in Infection Control and Epidemiology	Ms. Linda Greene
Council of State and Territorial Epidemiologists	Ms. Carole VanAntwerpen
HICPAC Surveillance Working Group	Dr. Daniel Diekema
Infectious Diseases Society of America	Dr. Edward Septimus
Society for Healthcare Epidemiology of America	Dr. Michael Klompas
Society of Critical Care Medicine	Drs. Clifford Deutschman, Marin Kollef, and Pamela Lipsett

- The Working Group recognized that there is currently no gold standard, valid, reliable definition for VAP. Even the most widely-used VAP definitions are neither sensitive nor specific for VAP. Therefore, the Working Group decided to pursue a different approach—development of a surveillance definition algorithm for detection of ventilator-associated events (VAEs). This algorithm will detect a broad range of conditions or complications occurring in mechanically-ventilated adult patients.
- Because the reliability of HAI definitions has become particularly important in recent years, the Working Group focused on definition criteria that use objective, clinical data that are expected to be readily available across the spectrum of mechanically-ventilated patients, intensive care units and facilities—in other words, criteria that are less likely to be influenced by variability in resources, subjectivity, and clinical practices—and that are potentially amenable to electronic data capture.

National Center for Emerging and Zoonotic Infectious Diseases
Division of Healthcare Quality Promotion



The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of the Centers for Disease Control and Prevention.

ACCP Announces New Headquarters, Learning Center

In May 2012, the American College of Chest Physicians announced the purchase of 5.25 acres of land in Glenview, Illinois, which will become the future site of the ACCP headquarters and innovation and learning center. The new, two-story, 48,530 square foot, state-of-the-art facility will showcase the latest technologic and learning advances, allowing the ACCP to expand to meet the changing needs of physicians in clinical practice by delivering more of the quality and innovative education that physicians in pulmonary, critical care, and sleep medicine have come to expect.

In a recent interview, ACCP Executive Vice President and CEO Paul A. Markowski, CAE, offered a more detailed view of the new ACCP headquarters and innovation and learning center, including key drivers behind the decision to build a new headquarters and what to expect in the new building.

What prompted the need for a new building and location?

PM: Early in 2010, several infrastructure discussions were held regarding the technology and electrical needs, heating and air conditioning systems, and other long-term maintenance issues that were arising due to the age of the ACCP headquarters building. To make sure that we were going to be making decisions that would have the greatest impact for the future of the ACCP, we engaged CBRE Commercial Real Estate Services to work with the senior management team on a process to review the future needs of the ACCP as they related to the headquarters building. This process was able to not only define our future requirements but also provide options for Board of Regents consideration. Options included looking at the current physical structure, including building an addition and retrofitting the interior; looking at existing property to retrofit through purchase or lease; and looking for available land for a build-to-suit headquarters. One of the key drivers for the future was the ability to provide our premier educational opportunities, specifically simulation education, in an environment that would provide for the best learning for physicians.

Why did ACCP choose Glenview, Illinois, as its new headquarters?

PM: The Board of Regents determined that the best decision was to find a location that provided space to support a headquarters building and innovation/learning center. The Board not only considered locations that would have ease of access from major transportation centers like O'Hare International Airport, but, more importantly, locations that provided for the best learning experience on a "campus" setting. After a thorough search of the Chicago and surrounding suburban areas, property at The Glen, located in Glenview, Illinois, was chosen.

The center will have the space and tools to develop an immersive year-round curriculum.

MR. MARKOWSKI

What will become of the current headquarters?

PM: The current ACCP headquarters, where ACCP has been located since 1991, will be put on the market sometime in early 2013 for sale. That would not preclude us from considering a leasing scenario, but our preference is to sell the current building.

Who was involved in the decision regarding the new building?

PM: A great deal of preliminary work involved in the decision to purchase land and build a new headquarters with an innovation and learning center was spearheaded by the senior management team. As the Board of Regents worked its way through the various options, a Board Building Committee was formed to work with staff to ensure that all issues were thoroughly vetted and discussed before making recommendations to the Board of Regents for approval. This has been a team effort from the beginning.

What are the key features of the new building?

PM: The building's learning center will bring the full educational spectrum together in one place, all geared to support the practicing clinician and advance chest medicine. Key features include:

- A large auditorium will support group meetings and didactic learning.
- Eight breakout rooms will enable focused training sessions or small-group problem solving.
- Six simulation labs will encourage teams of caregivers to integrate and apply new techniques in a realistic environment.

Using on-site wet and dry labs, ACCP staff will develop new, innovative tools for training and educational support, from iPad® apps to robotics to artificial fluids for better simulation. No other medical society works so closely with subject matter experts to design and implement practical educational tools—but the ACCP knows how important it is to bring members' expertise to scale: it could be the innovation that saves a patient's life.

How will the new building and features impact the education that ACCP provides?

PM: The College's innovation and learning center will feature an integrated, comprehensive curriculum, far beyond anything else available. Bringing together specialists from the three key respiratory health fields—pulmonology, critical care, and sleep medicine—it will dramatically enhance the education members receive at the annual CHEST meeting and elsewhere and help them adapt to the rapidly changing health-care landscape.

The innovation and learning center will mix expert lecture with problem-based learning, self-study, a state-of-the-art simulation center, and ongoing tools to continue measuring and improving performance. This will give care teams a full-fledged educational experience that not only immerses them in new material but also gives them the individual and group training to immediately put what they learn into practice for the benefit of their patients.

The center will be equipped with the space and tools to develop an immersive year-round curriculum. The ACCP plans to address the full range of problems, procedures, and treatments in order to provide the information members need to help every type of patient they treat.

Just as important, the innovation and learning center will also create an interactive campus for chest specialists from throughout the world. Backed by the trusted educational expertise of the ACCP, the center's welcoming environment will promote exchange and innovation with leaders in the field and the next generation of care providers. By bringing them together in one transformative place, the College can encourage the innovations that ripple well beyond its walls—and, ultimately, advance respiratory health and medicine for all.

How will the new features allow ACCP to build sustainable revenue?

PM: In our current location, we have not been able to accommodate the number of simulation course attendees needed to advance our cost-effectiveness. We have also been limited by the number of days during the year that we could offer such

Continued on following page

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courses. We expect to fully utilize the capacity of the center not only with our course offerings, but we will be able to offer the center to other medical specialty organizations. We expect that the center will be able to not only provide us with additional revenue but will allow us to grow and expand our educational offerings worldwide.

How will OneBreath® be integrated into the new building?

PM: The ACCP OneBreath campaign is the entry point for any patient, health-care provider, or anyone who has a personal connection to better lung health. The new facility will allow us to expand our educational development and offerings for patients, health-care providers, and the general public.

How is the new building being funded? How can ACCP members participate in this new endeavor and support the future of ACCP?

PM: The decision to buy land and build the new innovation and learning center and office building was based on the current solid financial position of the ACCP. This decision was not predicated on any brick and mortar capital campaign. However, the opportunity for our members, partners, and others to participate in this exciting new expansion of the ACCP drove us to explore avenues for this participation. At CHEST 2012 in Atlanta, you will hear more about the *Beyond Our Walls: Advancing the Future of Chest Medicine* campaign that The CHEST Foundation is spearheading. We look forward to everyone's participation in the campaign.

For more information about the campaign, contact Marilyn Lederer, CPA, Executive Director of The CHEST Foundation, at mlederer@chestnet.org.

When does the ACCP expect to move into its new location and host its first education course?

A new, two-story, 48,530 square foot, state-of-the-art facility will showcase the latest technologic and learning advances, allowing the ACCP to expand to meet the changing needs of physicians in clinical practice.

PM: We have all been working extremely hard to make sure that we are meeting all timelines that will allow us to move into our new home by October 1, 2013, just in time for CHEST 2013 in Chicago, taking place October 26-31. The ACCP will not waste time in providing our first courses. You can look for course offerings to begin late in the winter of 2013.

How will the new location and features allow ACCP to continue to fulfill its mission?

PM: For more than 75 years, the American College of Chest Physicians and its members have worked together to improve clinical care, promote public awareness, and lead the way forward in lung and heart health. As national reform and technologic breakthroughs rapidly change the world of medicine in unforeseen ways, a modern, adaptable center for innovation and education is no longer optional—it's essential.

We will not only be fulfilling our mission but enhancing it through a state-of-the-art educational environment that keeps involved clinicians on the leading edge; helps the next generation become the first-rate professionals we need; incubates new ideas, practices, and techniques; and spurs the transformation of respiratory care and health around the world.

We all know that every breath is precious—and together, we can help everyone breathe easier. ■

DATA WATCH

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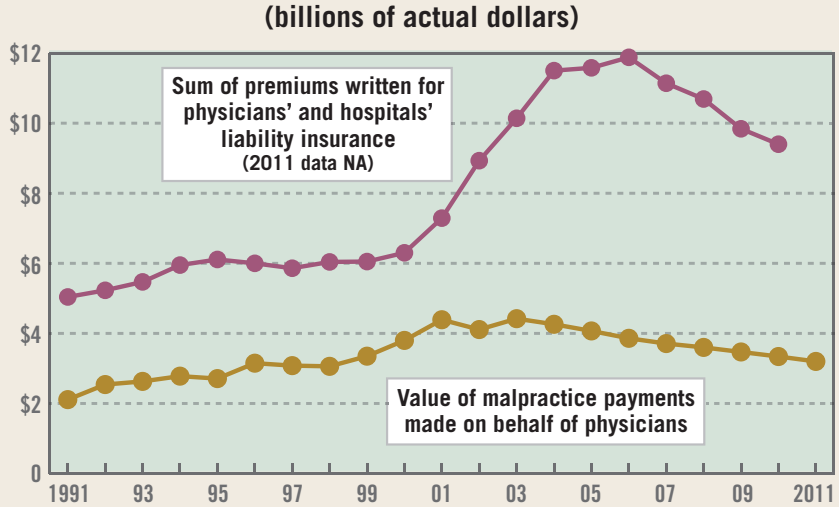

Note: Based on data from the National Practitioner Data Bank and A.M. Best & Co.
Source: Public Citizen

IMNG Medical Media

Pulmonary Perspectives

Gender Differences in COPD: Do They Still Matter?

An ongoing concern has been whether women with COPD are less frequently diagnosed.

COPD is currently the third leading cause of mortality in the United States (Heron M. National vital statistics reports; vol 60(6). Hyattsville, MD: National Center for Health Statistics 2012, http://www.cdc.gov/nchs/data/nvsr/nvsr60/nvsr60_06.pdf), but this burden is disproportionately shared by women. COPD-related deaths in the United States among women now outnumber those of men (Han et al. *Am J Respir Crit Care Med.* 2007;176[12]:1179). While it is tempting to presume that this is completely attributable to a relative increase in tobacco use among women, there are epidemiologic and biological data supporting the idea that COPD disease presentation and progression may differ in women, revealing significant opportunities to improve clinical care and consider new avenues for research.

Diagnosis

An ongoing concern has been whether women with COPD are less frequently diagnosed. Two studies with similar design have attempted to answer that question. In the first, when a clinical vignette suggestive of a diagnosis of COPD was presented to physicians, the diagnosis of COPD was less frequent when the subject was a woman (Chapman et al. *Chest.* 2001;119[6]:1691). In the second study, published 5 years later, the gender discrepancy in diagnosis disappeared when physicians were presented with spirometry (Miravitlles et al. *Arch Bronconeumol.* 2006;42[1]:3). These data underscore the importance of obtaining spirometry data to counter the risk of physician gender bias in diagnosis of the disease. Furthermore, the implications for diagnosis in women may be even more important for women than men. A meta-analysis of 11 longitudinal studies concluded that for the same amount of tobacco smoked, women experienced a greater rate of lung function decline (Gan et al. *Respir Res.* 2006;7:52). The Lung Health Study also demonstrated more rapid lung function decline in women who continued to smoke but, importantly, an even greater potential to recover lung function after smoking cessation compared with men (Bjornson et al. *Am J Public Health.* 1995;85[2]:223). Unfortunately, multiple studies have also concluded that smoking cessation is actually more difficult for women to achieve and maintain (Han et al. *Am J Respir Crit Care Med.* 2007;176[12]:1179).

Biological Basis

DR. CARLOS MARTINEZ

DR. MEILAN HAN

There may be a biological basis to differences in tobacco susceptibility. Each cigarette smoked may represent a relatively higher "dose," given that women are, on average, smaller than men. Clinical studies suggest that the plasma clearance of nicotine is also lower in women than men; women may have lower capacity for DNA repair than men and are more prone to oxidative damage (Rivera et al. *Clin Chest Med.* 2004;25[2]:391). Adipokines have also recently gained interest as potential mediators in the deregulated pro- and anti-inflammatory balance responsible for the development of COPD, with both systemic and bronchial leptin levels being associated with the disease and with more severe local inflammation (Assad et al. *Biochimie.* 2012 Mar 14 [epub ahead of print]). New evidence points toward a stronger association between leptin levels and other inflammatory markers in women with COPD than men (Breyer et al. *Respir Med.* 2011;105[7]:1046).

Mortality Rates

Conflicting data exist regarding differences in mortality rates between men and women with COPD. A recent analysis of the TORCH study demonstrated that women, in general, had lower all-cause mortality, which is consistent with population-based data. However, after adjusting for baseline variables, including FEV_1, BMI, geographic region, and history of myocardial infarction, the difference was no longer statistically significant (Celli et al. *Am J Respir Crit Care Med.* 2011;183[3]317). While respiratory-related deaths were the most frequent cause of death, overall, the causes of death appeared to be similarly distributed between men and women.

Symptom Differences

One of the most interesting and ubiquitous findings in women with COPD is a lower frequency of phlegm production (de Torres et al. *Chest.* 2005;128(4):2012), even when the frequency of cough is similar or higher and the reported dyspnea more severe (Celli et al. *Am J Respir Crit Care Med.* 2011;183[3]: 317). Women are also under-represented among patients with a chronic bronchitic COPD phenotype (Kim et al. *Chest.* 2011;140[3]: 626). The differences in phlegm and bronchitic symptoms, in general, are intriguing, as among advanced COPD subjects in the National Emphysema Treatment Trial (NETT), women exhibited less radiologic emphysema and smaller airway lumen area with thicker bronchial walls as compared with men (Martinez et al. *Am J Respir Crit Care Med.* 2007;176[3]:243). Studies also suggest women report more severe dyspnea during exercise as compared with men with similar lung function (de Torres et al. *Respir Res.* 2007;8:18), but the reasons for this are still not well understood.

Quality of Life

Gender differences are also evident in personal experiences from COPD. In mild to moderate COPD, quality of life (QOL) is significantly worse among women (Celli et al. *Am J Respir Crit Care Med.* 2011;183[3]:317), and the factors related to poorer QOL in women are also not well understood. In trying to understand factors that predict QOL, a combination of dyspnea, exercise capacity, and comorbidities were significantly associated with QOL in men with COPD. In women, however, only dyspnea and oxygenation were significant predictors of QOL (de Torres et al. *Health Qual Life Outcomes.* 2006;4:72). Evidence from other chronic diseases (Ng et al. *Womens Health Issues.* 2010;20[5]:316) suggests that a patient's experience with the medical system and their relationship with their health-care provider may also contribute to gender differences in a patient's experience of the disease. Differences in comorbidities may also contribute to variation in QOL (Ninot et al. *Heart Lung.* 2006;35[2]:130). In general, women with COPD report more anxiety, depression, obesity, and physician-diagnosed osteoporosis than men (Almagro et al. *Respir Med.* 2010;104[2]:253). Another factor that may also contribute to gender discrepancies in QOL is the finding that women report more frequent exacerbations. This has been documented in several large clinical trials, including TORCH (Celli et al. *Am J Respir Crit Care Med.* 2011;183[3]:317), UPLIFT (Tashkin et al. *Respir Med.* 2010;104[10]:1495) and the NIH-sponsored azithromycin in COPD trial (Albert et al. *N Engl J Med.* 2011;365[8]:689). Whether this is due to a difference in reporting threshold or disease biology is unknown, but it is a topic worthy of further investigation.

Medications

Importantly, these trials did not demonstrate significant differences in the efficacy of the therapies being studied, including tiotropium, fluticasone/salmeterol, and azithromycin, respectively. However, it is only recently that gender differences in therapeutics have even been examined. It was 1994 when the US National Institutes of Health issued a guideline that gender differences in clinical trials must be evaluated to ensure the safety and efficacy of the drug in all of the patients who might be receiving that drug (*Federal Register* of March 28, 1994; FR 59 14508-14513). Prior to 1994, women had been largely excluded from drug studies due to safety concerns. Even if data up to this point suggest that existing pharmacotherapies for COPD are equally efficacious in men and women, it is important that we continue to examine the efficacy of all future medications developed for COPD in both men and women. In our quest to define personalized medicine for COPD, gender-related differences can be exploited to help us better understand the disease and must remain an important consideration in our future approach to diagnosis, prognosis, therapy, and research.

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UNIVERSITY OF SOUTH CAROLINA SCHOOL OF MEDICINE

Division Chief Opportunity

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Study Results Challenge VTE Pathophysiology

Individual analysis shows differences in risk factors of DVT vs. PE.

BY ELIZABETH MECHCATIE
IMNG Medical News

Post-trauma deep vein thrombosis and pulmonary embolism diagnoses in severely injured blunt trauma patients were associated with different clinical risk factors, leading researchers to consider that the two "may represent distinct pathophysiologic entities."

Dr. Scott C. Brakenridge also pointed to other recent findings, including a study that found that more than half of pulmonary embolism (PE) cases are diagnosed within the first few days of injury (Am. J. Surg. 2011;201:209-15). He spoke at the annual Meeting of the American Association for the Surgery of Trauma.

"We believe these findings bring into question whether the conventional wisdom of peripheral thrombosis and subsequent embolism is an oversimplification of thromboembolic pathophysiology after injury," said Dr. Brakenridge, a trauma/surgical critical care and vascular surgery fellow, at Harborview Medical Center and the University of Washington, Seattle.

In the multicenter prospective observational study, he and his coinvestigators compared clinical risk factors for deep vein thrombosis (DVT) and PE in 1,882 severely injured blunt trauma patients with evidence of hemorrhagic shock, treated at one of five urban trauma centers from 2002 to 2011. Most were male, their median age was 41 years, and the median injury severity score was 33; they received a mean of 6 U of packed red blood cells and 12 L crystalloid resuscitation over the first 24 hours.

Link between peripheral thrombosis and subsequent embolism may be oversimplified.

DR. BRAKENRIDGE

Within 28 days of injury, 95 patients (5.1%) were diagnosed with a DVT and 73 (3.9%) were diagnosed with a PE; the total number of patients diagnosed with the traditional composite end point of venous thromboembolism (VTE) was 159 (8.5%). Of the 159 patients with VTE, only 6% (9 patients) were diagnosed with both DVT and PE.

Risk factors for the composite end point VTE resembled those from other studies. However, when analyzed individually, DVT and PE exhibited differences in their risk-factor profiles. The independent risk factors identified among those diagnosed with a DVT were failure to initiate prophylaxis within the first 48 hours, a thoracic abbreviated injury score of 3 or more, and body mass index above 28 kg/m^2. Independent risk factors for PE were serum lactate greater than 5 mmol/L and male gender. The median times to diagnosis of DVT and PE were similar at approximately 10 days.

These results indicate that the risk factors for a clinical DVT diagnosis after severe blunt trauma "appear to represent the inability to initiate prompt pharmacologic prophylaxis, overall injury burden and obesity, while risk factors for PE are gender specific and consistent with a severe shock state." Dr. Brakenridge said.

Mechanistically, he and his associates are suggesting that while a predisposition to DVT and PE may share "a postinjury hypercoagulopathic state … their discordance may be secondary to differences in local factors such as tissue injury, stasis, and endothelial damage, as well as systemic influences such as a severe shock state," he added.

The study had limitations, including a lack of standardized DVT screening protocols, and more prospective studies that evaluate the pathophysiology, diagnosis, and treatment of DVT and PE early after injury are needed, Dr. Brakenridge said.

"If borne out in future prospective studies, this could have significant implications for the diagnosis, and treatment of postinjury DVT and PE," he added.

The study had limitations, including a low event rate, and more prospective studies that evaluate the pathophysiology, diagnosis, and treatment of DVT and PE early after injury are needed, Dr. Brakenridge said.

Replication and confirmation of their results "could have significant implications for the diagnosis, and treatment of postinjury DVT and PE," he added.

Dr. Brakenridge and his coinvestigators reported having no relevant financial conflicts. ■

Longer In-Hospital CPR Nets Benefits

BY MARY ANN MOON
IMNG Medical News

Systematically lengthening the duration of resuscitation efforts for patients who have in-hospital cardiac arrests could improve survival with no adverse impact on neurological status, according to researchers.

In a study of 64,339 patients who had in-hospital cardiac arrests at 435 U.S. hospitals over an 8-year period, this survival benefit was independent of numerous patient factors, wrote Dr. Zachary D. Goldberger of the division of cardiovascular medicine, University of Michigan, Ann Arbor, and his associates. The report was published in The Lancet.

Importantly, they wrote, neurologic status was not affected by the duration of resuscitation efforts, so patients revived after relatively long CPR attempts of 30 minutes or more were as neurologically intact as were those revived after brief attempts of less than 15 minutes.

"Our most notable result was that long resuscitation attempts might be linked to increased rates of return of spontaneous circulation and survival to discharge," they said.

At present, resuscitation guidelines do not address the issue of when to terminate such efforts, and there are not enough data available to guide practice. "Clinicians are frequently reluctant to continue efforts when return of spontaneous circulation does not occur shortly after initiation of resuscitation, in view of the overall poor prognosis for such patients," the researchers noted.

They examined the issue using information from the Get With the Guidelines–Resuscitation database, the largest registry of in-hospital cardiac arrests in the world. A total of 31,198 patients (48.5%) achieved return of spontaneous circulation, while 33,141 (51.5%) died after termination of resuscitation efforts.

Approximately 80% of patients who survived to hospital discharge had favorable neurologic status. The rate of favorable status did not differ significantly by duration of resuscitation: It was 81.2% for patients in whom resuscitation attempts lasted less than 15 minutes, 80.0% for those in whom resuscitation attempts lasted 15-30 minutes, and 78.4% for those in whom resuscitation attempts lasted longer than 30 minutes.

As expected when there is no consensus on the appropriate duration of resuscitation attempts, the investigators found wide variation among hospitals in this practice.

Overall, the median duration of resuscitation efforts was 17 minutes. When the hospitals were divided into quartiles based on this duration, those in the quartile with the shortest interval had a median duration of 16 minutes, while those in the quartile with the longest interval had a median duration of 25 minutes.

VITALS

Major Finding: The rate of favorable neurologic status was 81.2% for patients in whom resuscitation attempts lasted less than 15 minutes, 80.0% with 15- to 30-minute attempts, and 78.4% with attempts lasting over 30 minutes.

Data Source: An observational analysis of survival outcomes in 64,339 patients who survived in-hospital cardiac arrest at 435 U.S. hospitals during 2000-2008.

Disclosures: This study was funded by the American Heart Association, the Robert Wood Johnson Foundation, and the National Heart, Lung, and Blood Institute. Dr. Goldberger reported no financial conflicts of interest, and one of his associates reported ties to Medtronic and United Health Care.

Resuscitation efforts lasted more than 50% longer at hospitals in the longest quartile compared with those in the shortest quartile.

Patients at the hospitals with longer durations of resuscitation efforts had significantly higher overall survival and significantly higher survival to hospital discharge than did those at hospitals with shorter durations of resuscitation efforts, Dr. Goldberger and his colleagues said (Lancet 2012 Sept. 4 [doi:10.1016/S0140-6736(12)60862-9]). The study findings suggest that standardizing resuscitation procedures and identifying a minimum duration could improve patient survival. "Prolongation of resuscitation attempts by 10 or 15 minutes might have only a slight effect on resources once efforts have already begun, but could improve outcomes," the investigators noted.

"We are unable to provide a specific cutoff from these data and are hesitant to speculate," especially because this was an observational study that cannot establish cause and effect. Moreover, several variables that almost certainly affected the duration of resuscitation efforts were not addressed in this study, such as the quality of chest compressions and the availability at each hospital of percutaneous intervention.

It is even possible that the duration of resuscitation attempts is merely a marker for "more comprehensive care" with longer CPR performed at centers where resuscitation guidelines are reliably implemented, they added.

It should also be noted that this study did not address long-term outcomes in survivors of resuscitation. "The extent to which critically ill patients benefit from survival months to years after cardiac arrest should be the ultimate measure of the usefulness of resuscitation measures," Dr. Goldberger and his associates said. ■

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Patients revived after 30 minutes of CPR were as neurologically intact as those revived after attempts of less than 15 minutes, investigators reported.

COMMENTARY

Dr. Jun Chiong, FCCP, comments: Prolonged resuscitation efforts have been shown to improve survival in various setting especially in the hospital and cardiac catheterization laboratory. Goldberger et al. was able to strengthen this in a study of 64,339 patients who had in-hospital cardiac arrests at 435 U.S. hospitals. It is also important to note that in our present value-based care system, functional outcome is as important as out-of-hospital survival due to the rising cost and lack of resources for long term care hospitals and facilities.

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