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Cutting exposure to secondhand smoke could prevent hundreds of thousands of heart attacks every year, according to researchers.

Smoking Bans Linked To Fewer Heart Attacks

BY MICHELE G. SULLIVAN
Elsevier Global Medical News

The rate of acute myocardial infarction in localities that imposed a ban on public smoking dropped by an average of 17% after 1 year, and by up to 41% within 3 years, two new meta-analyses demonstrated.

Using the same epidemiologic studies from the North America and Europe, two sets of authors came to identical, independent conclusions: Cutting exposure to secondhand smoke could prevent hundreds of thousands of hearts attacks every year in the United States alone.

"If this association represents a cause-and-effect relationship, and assuming approximately 920,000 incident acute myocardial infarctions every year in the U.S., a nationwide ban on public smoking might ultimately prevent as many as 156,400 new acute MIs yearly," Dr. David G. Meyers wrote in the Sept. 29 issue of the Journal of the American College of Cardiology.

The public health implications of the two meta-analyses, which included data from more than 24 million people, can't be ignored, said James M. Lightwood, Ph.D., whose article appeared in the Oct. 6 issue of Circulation: Journal of the American Heart Association. "This analysis shows … that passage of strong smoke-free legislation produces rapid and substantial benefits in terms of reduced myocardial infarctions, and that these benefits grow with time," wrote Dr. Lightwood of the University of California–San Francisco, and his co-authors (Circulation 2009 [doi:10.1161/CIRCULATIONAHA.109.870691]).

Dr. Meyers of the University of Kansas, Kansas City, and his colleagues examined 11 studies that looked at the rates of acute myocardial infarction before and after the passage of public smoking bans. Six of the studies were U.S.-based, one was from Canada, and four were from Europe. The post-ban observation periods ran from 2 months to 3 years and included data from one city

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Meta-Analysis: PAH Therapies Cut Mortality by 43%

Hospitalization rate reduced by 61%.

BY BRUCE JANCIN
Elsevier Global Medical News

BARCELONA — Targeted therapies for pulmonary arterial hypertension collectively reduced all-cause mortality by 43% compared with placebo, in a meta-analysis of the randomized, placebo-controlled, clinical trials conducted during the last 18 years.

Moreover, treatment reduced by 61% the hospitalization rate for pulmonary arterial hypertension (PAH), an end point with major economic and quality of life consequences, Dr. Nazzareno Galiè noted at the annual congress of the European Society of Cardiology.

These findings, while highly significant both statistically and clinically, probably underestimate the true magnitude of treatment benefit in clinical practice, because the meta-analysis included negative trials of drugs subsequently denied marketing approval due to lack of efficacy, such as beraprost and terbogrel, as well as studies of approved drugs in nonapproved, suboptimal doses.

"This is a very, very conservative approach," said Dr. Galiè, professor of cardiology and head of the pulmonary hypertension center at the University of Bologna (Italy).

The meta-analysis offers a rebuttal to critics who claim current therapies for PAH provide only marginal clinical benefit. The critics have trumpeted another meta-analysis that concluded the treatments produced "limited benefits in clinical end points" and failed to support a significant survival advantage (Am. Heart J. 2007;153:1037-47). But this was a seriously flawed meta-analysis that missed six randomized trials available at the time, according to Dr. Galiè.

See **Meta-Analysis** • *page 2*

INSIDE

Acute PE Predictors Point to ICU Admits

BY BRUCE JANCIN
Elsevier Global Medical News

NEW ORLEANS — The best predictors of in-hospital deterioration of patients diagnosed with acute pulmonary embolism in the emergency department are a shock index greater than 1 and a pulmonary embolism severity index score more than 100, according to data from the EMPEROR registry.

The clinical implications: Calculate the pulmonary embolism severity index (PESI) and shock index routinely in patients with pulmonary embolism. And strongly consider admission to an ICU for those patients having values above the thresholds, Dr. Jeffrey A. Kline said at the annual meeting of the Society for Academic Emergency Medicine.

He analyzed the prognostic accuracy of five predictors of in-hospital adverse events in 2,188 consecutive patients diagnosed with pulmonary embolism in 22 EDs participating in the landmark EMPEROR (Emergency Medicine Pulmonary Embolism

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Better PAH Treatment Still Needed

Meta-Analysis • *from page 1*

The 21 randomized placebo-controlled trials included in the meta-analysis by Dr. Galiè and coworkers involved 3,140 PAH patients followed during an average of 14.3 weeks of treatment. The trials involved endothelin-receptor antagonists, thromboxane synthase inhibitors, prostanoids, and phosphodiesterase type-5 inhibitors.

"Interestingly enough, there are four times more commentaries and editorials than there are randomized studies," the cardiologist noted.

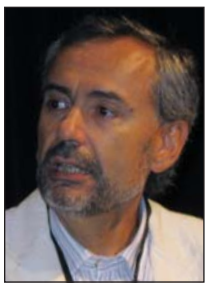
All-cause mortality occurred in 1.5% of patients in the active treatment arms, compared with 3.8% of placebo-treated controls. That translated into a need to treat 61.2 patients for 14.3 weeks to prevent one death. The PAH hospitalization rate was 3.2% in the active treatment groups and 8.0% in controls, for a number needed to treat of 19.9.

The database was not of sufficient size to show any significant differences in efficacy for the various drug classes, according to Dr. Galiè.

Six-minute walk distance improved with active treatment by a mean of 11% over baseline, or just under 36 meters, in the 19 randomized trials reporting this end point.

Small to moderate improvements in various hemodynamic parameters with active treatments were also identified via right heart catheterization. Among these were a 1.84-mm Hg weighted mean reduction in right atrial pressure.

"This is the first time a statistically significant decrease in right atrial pressure has been shown. It is not all that much, but there is no single randomized controlled study with a significant reduction in right atrial pressure," Dr. Galiè said.



Although the meta-analysis showed a treatment benefit, mortality over the intermediate and long term remains high.

DR. GALIÈ

There were also weighted mean reductions of 2.86 mm Hg in pulmonary arterial pressure and 4.09 resistance units in pulmonary vascular resistance, along with a mean increase of 0.18 L/min per m^2 in cardiac index.

Although this meta-analysis refutes the argument that current treatments for PAH bring little clinical benefit, Dr. Galiè was quick to point out he considers these therapies inadequate. Mortality over the intermediate and long term remains high, and many patients have extensive hemodynamic and functional impairments despite treatment.

The meta-analysis was funded by the University of Bologna. Dr. Galiè disclosed having served on advisory boards for Actelion, Pfizer, Eli Lilly & Co., United Therapeutics, Bayer-Schering, GlaxoSmithKline, and Encysive. ■

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Smoke-Free Laws Advocated

Smoking Ban • *from page 1*

that rolled back its ban after 6 months (J. Am. Coll. Cardiol. 2009;54:1249-56).

That study, in Helena, Mont., revealed the speed with which both the ban and its suspension affected heart attack rates, Dr. Meyers noted. Over the 6-month ban, incident acute MI rates dropped 40%. After the ban was rescinded, the rate returned to baseline.

A study in Pueblo, Colo., indicated that time may potentiate a ban's effect. Over a 3-year follow-up period, the town experienced a 41% reduction in the rate of acute MI. Monroe, Ind., with a follow-up of 8 months, saw a 50% decrease, with nonsmokers accruing most of that benefit—their rate of admission for acute MI dropped by 70% over the study period.

Not all of the studies examined had such robust results, however.

The public smoking ban in the state of New York was followed by an 8% MI decrease over 1 year. Three studies in Italy also had modest results, with no decrease in acute MI in Rome over 1 year and a 2% increase in the Piedmont region over 6 months.

In the Piedmont study, however, the investigators did report a 25% decrease in acute MI among women younger than 60 years. The ban had other positive effects, Dr. Meyers and his coauthors added: "Nicotine vapor in public places decreased 90%-95%, cigarette sales declined 8.9%, and cigarette consumption decreased 7.6%."

When the authors analyzed all the data, they concluded that the overall risk reduction associated with a public smoking ban was 17% (RR 0.83). "The beneficial effect of smoking bans seems to be rapid, with declines in acute MI incidence within 3 months," wrote Dr. Meyers and his coauthors. "Among smokers, incident acute MI is reduced within days after smoking cessation. In nonsmokers, even brief exposure to secondhand smoke has been associated with changes in platelet activation, vascular elasticity, endothelial function, heart rate variability, and lipid metabolism, supporting the biological plausibility of smoking bans' effects on acute MI."

Dr. Lightwood and his colleagues examined the same 11 studies, with 2 additional studies—1 from Massachusetts (RR 0.82) and 1 from Ireland (RR 0.89). His pooled random-effects model estimated that the overall decrease in acute MI associated with a pubic smoking ban is 17% (RR 0.83), and that the benefit grows with time, reaching 36% by 3 years.

"While we obviously won't bring heart attack rates to 0, these findings give us evidence that in the short- to medium-term, smoking bans will prevent a lot of heart attacks," Dr. Lightwood said in a statement. "This study adds to the already strong evidence that secondhand smoke causes heart attacks and that passing 100% smoke-free laws in all workplace and public places is something we can do to protect the public."

Cardiologists and other physicians should view the studies as a call to action, Dr. Steven A Schroeder of the University of California–San Francisco said in an editorial (J. Am. Coll. Cardiol. 2009;54:1256-7).

"It is prudent to assume that exposure to secondhand smoke is almost as dangerous to persons with diagnosed or latent coronary disease as active smoking.," he wrote. "Therefore, cardiologists should expand their clinical repertoire to include screening and counseling for secondhand smoke exposure, just as they screen for lipid disorders." ■

CHEST PHYSICIAN

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 and Elsevier Global Medical News. Content for NEWS FROM THE COLLEGE is provided by the American College of Chest Physicians.

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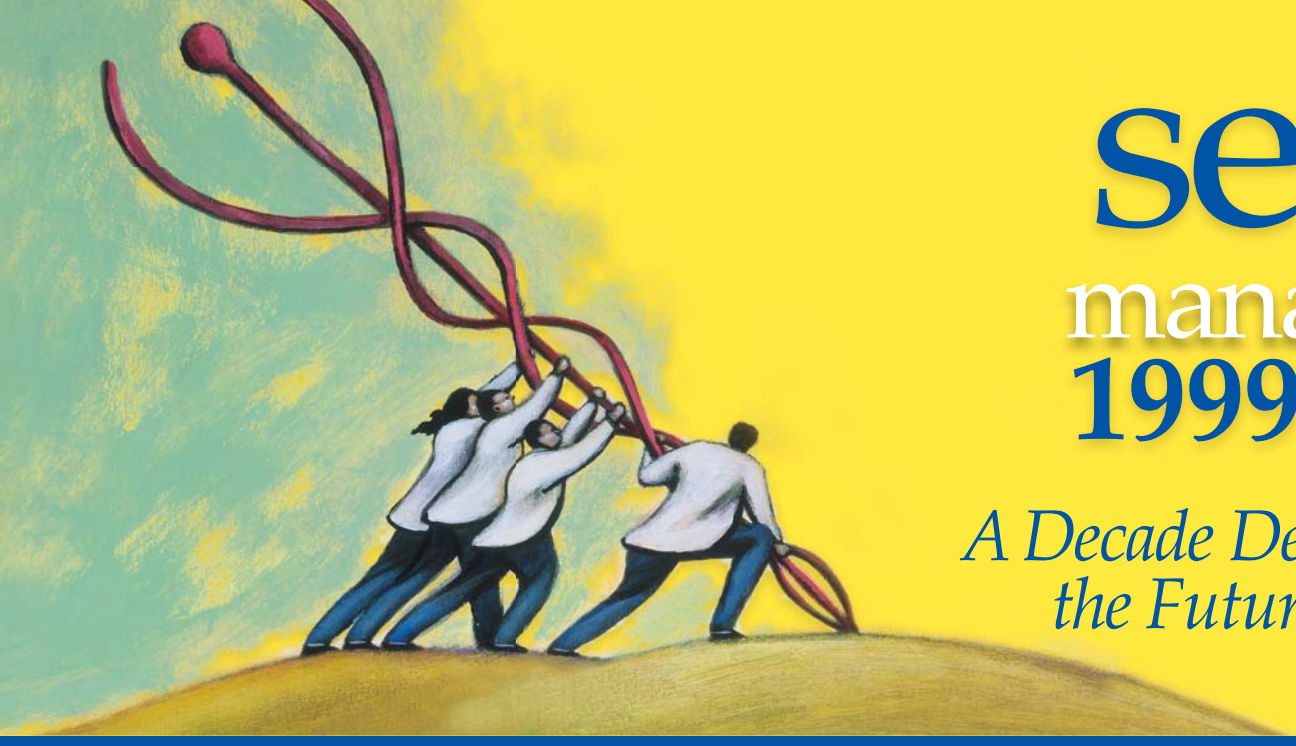

sepsis management 1999 *to* 2009

A Decade Devoted to Survival & the Future of Patient Care

An Interactive Educational Symposium held at

CHEST 2009
San Diego, CA
October 31-November 5

Monday, November 2, 2009, 5:30 PM - 10:00 PM
Manchester Grand Hyatt San Diego, Elizabeth Ballroom DE

Overview Despite significant changes in the treatment of sepsis as a result of new therapies and guidelines launched over the past decade, sepsis incidence and mortality remain high. Early identification and treatment of the septic patient continue to pose significant challenges. This symposium will explore the evolution of sepsis management from a patient perspective, providing an overview of developments in patient care over the past 10 years—from landmark sepsis trials to recent advances, including the application of biomarkers to sepsis patient management. The latest proposals on sepsis definitions and an overview of the latest sepsis trials will be presented. The interactive session will conclude with an open panel discussion.

Intended Audience This symposium is intended for physicians, doctors of pharmacy, and physician extenders such as nurse practitioners and physician assistants, who deal with patients with sepsis. This includes those with practices in pulmonology, critical care medicine, cardiothoracic surgery, pediatric pulmonology, neonatology, and pediatric critical care medicine.

Faculty

Carl Flatley, DDS, MSD
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James M. O'Brien, Jr., MD, MSC, FCCM
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Columbus, OH

Agenda

5:30 PM	**Registration, Wine & Cheese Reception, Meet the Faculty**
6:30 PM	**The Septic Patient: A Father's Perspective**
6:50 PM	**Treating the Septic Patient: The Past 10 Years**
7:10 PM	**Landmark Trials Impacting Clinical Practice**
7:30 PM	**Use of Biomarkers in Diagnosing and Monitoring Sepsis**
7:50 PM	**Clinical Applications of Procalcitonin® (PCT) in Critical Care**
8:10 PM	**Procalcitonin for Antibiotic Stewardship in Respiratory Tract Infection**
8:30 PM	**Patient Case Studies: Clinical Challenges and the Role of Procalcitonin**
8:50 PM	**New Perspectives in Defining Sepsis**
9:10 PM	**Panel Discussion: The Future of Sepsis Research**
9:30 PM	**Q&A**
	Complimentary Drinks, Dinner & Dessert Served

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Vaccinating 70% of U.S. Could Curb H1N1 Flu

Research is needed to examine the logistics of vaccination with a limited vaccine supply.

BY HEIDI SPLETE
Elsevier Global Medical News

Vaccination of 70% of the United States population—starting with children—could mitigate a severe epidemic of the pandemic influenza A(H1N1) virus, according to data from simulation models and analyses of existing studies. The research was published Sept. 10 in Science Express, the early online edition of the journal Science.

"So far, in the U.S.A. and most parts of the upper northern hemisphere, pandemic H1N1 has caused outbreaks in close-contact groups of children in schools or camps and has spread readily in households when introduced, but does not appear to be community wide," Yang Yang, Ph.D., of the Center for Statistics and Quantitative Infectious Diseases at the Fred Hutchinson Cancer Research Center in Seattle, and colleagues wrote.

The researchers devised models for two scenarios: prevaccination of all age and risk groups before the pandemic influenza A(H1N1) virus becomes widespread in the United States, and phased vaccination (either universal or starting with children) over time as the epidemic progresses.

Phased vaccination starts either at the beginning of the spread of disease or after a 30-day delay.

All the vaccination strategies studied that involved a 70% coverage rate could have a significant mitigating effect on an H1N1 epidemic, the researchers said. "Clearly, combining vaccination with other mitigation measures, such as social distancing and targeted use of antiviral agents, could be quite effective," they wrote (Science 2009; [doi:10.1126 /science.1177373]).

Based on the patterns of disease so far, a child-first phased vaccination plan would need to begin no later than mid-September in order to have a mitigating effect on this season's pandemic H1N1 illnesses, the researchers said. But an October vaccination could still make a difference if the epidemic peaks in November or December. "Phased vaccination has a potentially large effect on reducing spread, but delays the epidemic peak only slightly," they noted.

The models in the study suggested that, with a 30-day delay after the spread of infection begins, a phased vaccination strategy starting with 70% of children aged 6 months to 18 years would mitigate an epidemic, as would a phased strategy that didn't prioritize children and didn't wait until 30 days into the spread of disease.

But the models suggested that a universal strategy with a 30-day delay would be less effective, the researchers noted.

COMBINING VACCINATION WITH OTHER MEASURES, SUCH AS SOCIAL DISTANCING, COULD BE QUITE EFFECTIVE.

Without knowledge of how well matched an H1N1 vaccine is to the virus, the researchers evaluated vaccination strategies involving both heterologous and homologous vaccines.

A universal prevaccination protocol with a homologous vaccine and 70% vaccination coverage would significantly mitigate an epidemic. A 50% vaccine coverage rate would mitigate an epidemic spread to levels similar to that of a relatively mild seasonal flu epidemic. But a 30% rate of coverage would not be effective, the researchers wrote.

In the event of a heterologous vaccine, a 70% prevaccination of school-aged children could be as effective as universal prevaccination with a homologous vaccine, they added.

The pandemic H1N1 virus is disproportionately affecting children, similar to the pattern of the influenza A epidemic in 1978-1979, the researchers said. Data from an outbreak of pandemic H1N1 at a New York high school last spring suggest that a school student could infect an average of 2.4 schoolmates, the researchers explained.

The Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices currently recommends prioritizing early supplies of pandemic influenza A(H1N1) vaccine for children older than 6 months, health care workers, young adults, and individuals at high risk for complications. More research is needed to examine the logistics of vaccination with a limited vaccine supply, the researchers said. ■

CDC Updates Guidelines For Influenza Season

BY HEIDI SPLETE
Elsevier Global Medical News

The Centers for Disease Control and Prevention has updated its guidelines for using antiviral medications to treat the seasonal and pandemic influenza A(H1N1) viruses, according to the CDC Web site.

The updated recommendations include guidance for clinicians about antiviral treatment for very young children, information about correct dosing using the oseltamivir (Tamiflu) dosing dispenser and recommendations for antiviral treatment for patients with neurocognitive and neuromuscular disorders.

► **Treating children younger than age 1 year.** Oseltamivir is not approved by the Food and Drug Administration for use in children younger than 1 year of age. But given this age group's increased risk for complications from the H1N1 virus, the CDC recommends a 5-day antiviral treatment dose with oseltamivir of 25 mg twice daily for children aged 6-11 months, 20 mg twice daily for children aged 3-5 months, and 12 mg twice daily for children younger than 3 months.

The CDC's recommendations for 10-day prophylaxis with oseltamivir are 25 mg once daily for children aged 6-11 months, 20 mg once daily for children aged 3-5 months, but oseltamivir is not currently recommended for prophylaxis for children younger than 3 months unless the situation is deemed critical.

The FDA issued an Emergency Use Authorization in April 2009 for the emergency use of oseltamivir in children younger than 1 year old.

► **Dispenser measurements.** The updated CDC antiviral recommendations caution clinicians and pharmacists that an oral dosing dispenser that comes with Tamiflu for oral suspension shows dose measurements in 30-mg, 45-mg, and 60-mg increments. These measurements use milligrams and match those currently recommended by the CDC for treatment or chemoprophylaxis against pandemic influenza H1N1 infection, but the prescription instructions may be listed in milliliters or teaspoons, which can lead to dosing errors.

► **Patients with neuromuscular or neurocognitive disorders.** The revised recommendations for those individuals who might benefit most from early treatment with antiviral therapy include patients with disorders that can increase the risk for aspiration, such as spinal cord injuries, seizure disorders, cognitive dysfunction, and other neuromuscular disorders, plus any disorders that "can compromise respiratory function or the handling or respiratory secretions."

The CDC Web site states that the recommendations should be considered an interim document, which will be updated as needed. For the latest information on the CDC's flu guidance and recommendations, visit www.cdc.gov or www.flu.gov. ■

H1N1 Influenza Virus Shedding Can Exceed 1 Week

BY MITCHEL L. ZOLER
Elsevier Global Medical News

Some patients with pandemic influenza A(H1N1) shed live virus a few days longer than commonly occurs with seasonal flu, according to a Canadian study with 100 patients.

But the public health implications of the finding aren't clear, Dr. Gaston De Serres said during a press briefing at the annual meeting of the Interscience Conference on Antimicrobial Agents and Chemotherapy.

The results show that it's not enough to isolate people infected with pandemic H1N1 flu for just a couple of days after they become sick or until their fever resolves. People "may be tempted to reduce their time at home [when infected by H1N1], but our results show that would not be wise," said Dr. De Serres, a medical epidemiologist at the National Public Health Institute of Quebec. On the other hand, it is a policy issue to say whether a reduced risk for contagion is worth increased social disruption from prolonged isolation of infected people, he noted.

The study focused on 43 patients who had symptomatic flu and who were culture positive for the pandemic virus. In this group, eight (19%) remained culture positive 8 days after their symptom onset. In contrast, all patients with seasonal flu are routinely culture negative a week after symptom onset. "We can say that H1N1 appears to be shed longer [than seasonal flu] but not much longer," said Dr. De Serres, who also is professor of epidemiology at Laval University, Quebec. All 43 H1N1 patients in the study were culture negative 10 days after symptom onset.

Another 57 family members of these cases had concurrent flulike symptoms, but all 57 were culture negative the first time they were tested. Adding these 57 to the first 43 produced a total of 100 patients apparently infected with H1N1, of whom 8 were culture positive a week after their illness began, establishing a minimum 8% rate for the persistence of H1N1 shedding beyond a week of infection. The rate might even be greater because all of the family members may not have been infected with H1N1.

Dr. De Serres cautioned that the findings do not indicate that all eight patients remained contagious at day 8. Contagion requires more than just the shedding of live virus; it also requires transmission of an adequate virus dose. The study didn't look at the amount of virus shed on day 8. People who shed live virus "may potentially be contagious; we're not saying they are contagious," Dr. De Serres said. ■

FDA Forms New Office to Regulate Tobacco Products

Officials at the Food and Drug Administration have launched the Center for Tobacco Products, the first step in implementing a landmark tobacco law enacted in June.

Under the law, the FDA was granted new responsibilities such as reviewing premarket applications for new and modified tobacco products, setting advertising restrictions, and regulating tobacco ingredients. The Center for Tobacco Products will take the lead in implementing the law.

The FDA will use $5 million in seed money from its 2009 budget to establish the center's administrative functions. Once the center is up and running, future funding will come from user fees paid by the tobacco industry.

The new center will be headed up by Dr. Lawrence Deyton of George Washington University in Washington, who is an internist and who has previously worked on tobacco and other public health issues at the Department of Veterans Affairs and the Health and Human Services department.

"I am eager for the challenge of leading the tobacco team at FDA," Dr. Deyton said in a statement. "This is a tremendous opportunity for us … to make progress in combating tobacco use—the leading cause of preventable death in the United States."

The new center joins FDA's five existing centers, including Drug Evaluation and Research, Biologics Evaluation and Research, Food Safety and Nutrition, Devices and Radiological Health, and Veterinary Medicine.

—Mary Ellen Schneider

Antiviral Treatment Improved Mortality in Severe Flu

BY DOUG BRUNK
Elsevier Global Medical News

SAN FRANCISCO — Antiviral treatment for severe seasonal influenza may reduce mortality in hospitalized patients, results from a large observational study showed.

"When people have very severe influenza and present later, say on day 3 or day 4, if they're still quite symptomatic and we treat them with antivirals, we might be able to save their life," Dr. Nelson Lee said in an interview during a poster session at the annual meeting of the Interscience Conference on Antimicrobial Agents and Chemotherapy.

Dr. Lee and his associates studied 760 patients aged 18 and older who presented with influenza at two hospitals in the Hong Kong area during 2007 and 2008. The researchers performed nasopharyngeal aspiration for immunofluorescent assay or enzyme immunoassay, followed by isolation of the virus. They prescribed oseltamivir upon diagnosis and used Cox proportional hazard models to analyze factors related to survival.

Overall, 71% of the patients had influenza A virus and 29% had influenza B virus. The mean age of the patients was 70 years, 60% had underlying chronic illnesses, and 78% were hospitalized with influenza-related complications. Of the 760 patients, 37 (5%) died from pneumonia, respiratory failure, or sepsis, and 36 (5%) required ventilator support, reported Dr. Lee, head of the division of infectious diseases at Prince of Wales Hospital, The Chinese University of Hong Kong.

Of the patients in the study, 52% received oseltamivir 75 mg twice a day for 5 days. Of these, 78% received treatment within 2 days after symptom onset and 95% received treatment within 4 days after symptom onset.

Multivariate analysis showed that patients who received oseltamivir had

significantly reduced in-hospital mortality, compared with those who did not receive the drug (3.8% vs. 6.0%).

"The treated patients had a better outcome, so the message is not to withhold the therapy if they're very sick and they present on day 3 or day 4," Dr. Lee said.

Factors associated with mortality among all patients were age greater than 70 years (adjusted hazard ratio of 3.45) and male gender (HR 2.53). Other factors included underlying major comorbidities such as heart failure; cerebrovascular, neoplastic, chronic liver, renal, and neurologic diseases; diabetes; ischemic heart disease; and use of immunosuppressants (HR 2.64). Further factors included cardiorespiratory complications such as pneumonia, bronchitis, exacerbation of chronic pulmonary diseases, respiratory failure, and acute cardiovascular or cerebrovascular events (HR 9.10).

'The message is not to withhold the therapy if they've very sick and they present on day 3 or day 4.'

DR. LEE

Dr. Lee acknowledged that the study's observational design is a limitation, "so there could be confounders."

The study was funded by the department of medicine and therapeutics at Prince of Wales Hospital, the Research Fund for the Control of Infectious Disease from the Food and Health Bureau of the Hong Kong SAR Government, People's Republic of China, and an unrestricted educational grant from F. Hoffman-La Roche Ltd. ■

Probiotics Didn't Reduce RTI Incidence

BY KERRI WACHTER
Elsevier Global Medical News

Probiotics do not appear to reduce the incidence of respiratory tract infections, though they may help reduce the severity and duration of these infections, based on a review of 14 published randomized clinical trials.

"The majority of RCTs [randomized clinical trials] included in this review indicate that the incidence of RTIs [respiratory tract infections] does not appear to be considerably influenced by prophylactic administration of probiotics, although probiotics may have a beneficial role in reducing the severity and duration of subsequent RTIs," wrote Dr. Evridiki K. Vouloumanou of the Alfa Institute of Biomedical Sciences, Athens, and colleagues. The study appears in the September issue of the International Journal of Antimicrobial Agents (2009; 34:197.e1-10).

Ten of the 14 trials showed no difference in the incidence of RTIs between patients on probiotics and those on placebo. In four of the trials, the incidence of RTIs was significantly lower in those on probiotics.

The authors reviewed RCTs exploring the use of probiotics to prevent or ameliorate RTIs that they identified through a literature search. Databases included PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and SCOPUS. The researchers searched for available trials up to Feb. 5, 2008. They identified 14 studies with 3,580 participants that met their quality criteria (Jadad score greater than 2).

Upper RTIs in the studies included common cold, acute otitis media, tonsillitis/tonsillopharyngitis, sinusitis, and recurrent sinusitis. Lower RTIs included bronchitis and pneumonia. Probiotics used in the trials included *Lactobacillus* spp., a strain of *Bifidobacterium longum*, combinations of *Lactobacillus* and *Bifidobacterium* species, and a nonpathogenic strain of *Enterococcus faecalis*. Six of the trials involved healthy children or infants, six included healthy adults, one involved children with RTI, and one involved adults with RTI.

"A significant reduction regarding the severity of symptoms of RTIs associated with probiotic treatment was found in five of six RCTs that provided relevant data," they wrote. There was no difference in symptom severity in the remaining trial.

Data on adverse events were reported in 10 of the trials. In six RCTs, no adverse events were noted that could be attributed to the probiotics. Three of the remaining RCTs included adverse events of minor clinical severity—nausea, bloating and diarrhea. However, in one RCT the development of dyspepsia prompted reduction in the amount of probiotic daily intake.

The authors reported that they have no relevant financial relationships. ■

Serum Procalcitonin Could Guide Antibiotic Use in LRTI

BY MARY ANN MOON
Elsevier Global Medical News

Use of serum procalcitonin levels to guide antibiotic therapy decisions in emergency department patients with lower respiratory tract infections led to less antibiotic exposure, compared with decisions that were guided by clinical guidelines, according to a recent report.

In a clinical trial comparing the two approaches in 1,359 consecutive patients, the rates of adverse clinical outcomes were comparable, said Dr. Philipp Schuetz of University Hospital Basel (Switzerland) and his associates.

Lower respiratory tract infection (LRTI) is one of the most frequent indications for antibiotic prescriptions, and as many as 75% of patients receive antibiotics "despite the predominantly viral origin of their infection," the researchers noted (JAMA 2009;302:1059-66).

Procalcitonin is released in response to bacterial but usually not viral infection, and serum levels correlate with illness severity.

Small studies have suggested that measuring serum procalcitonin helps to estimate the probability that LRTI has a bacterial origin and merits antibiotic treatment.

Dr. Schuetz and his colleagues conducted a trial in six Swiss tertiary care hospitals, in which patients presenting to the emergency department with LRTI were randomly assigned to receive antibiotics according to their procalcitonin level (671) or according to conventional evidence-based guidelines (688).

The study was supported in part by BRAHMS Inc., manufacturer of the procalcitonin assay.

The patients had a wide range in the type and severity of infection. A total of 68% were diagnosed with community-acquired pneumonia, 17% had exacerbation of COPD, 11% had acute bronchitis, and 4% were found to have a noninfectious source of illness such as congestive heart failure or pulmonary embolism.

In the intervention group, procalcitonin was measured at presentation with a rapid assay that provided results in less than 20 minutes. Depending on the results, antibiotic therapy was strongly discouraged, discouraged, encouraged, or strongly encouraged. Procalcitonin levels were reassessed after 3, 5, and 7 days, and the results guided recommendations for discontinuing the antibiotics.

The primary end point—a composite of several adverse outcomes within 30 days of admission—was reached in 15% of the procalcitonin group and 19% of the control group, demonstrating noninferiority. The likelihood of developing an adverse outcome also was lower with procalcitonin-guided therapy in all the subgroups of patients studied, the investigators said.

Compared with the control group, the rate of antibiotic prescriptions was significantly reduced in the procalcitonin group (88% vs. 75%) among all the patients as a whole and in all subgroups.

If procalcitonin-guided use of antibiotics is widely adopted, it "will have substantial clinical and public health implications to reduce antibiotic exposure and associated risks of adverse effects and antibiotic resistance," Dr. Schuetz and his colleagues said.

In an editorial accompanying the report, Dr. Donald M. Yealy and Dr. Michael J. Fine of the University of Pittsburgh said that "several issues must be carefully considered before broadly translating this research into clinical practice."

First, the study had a high proportion of patients with pneumonia (68%), and most had severe disease.

"In such patients, the high likelihood of bacterial disease and high disease acuity render procalcitonin guidance unlikely to alter the decision to initiate antibiotic therapy and unlikely to augment the standard severity assessment of the patient," Dr. Yealy and Dr. Fine said (JAMA 2009;302:1115-16).

In addition, mortality was slightly higher in the group with procalcitonin-guided therapy (5.1%) than in the controls (4.8%).

This is consistent with an absolute mortality difference of 2.5%, which could prove to be important, Dr. Yealy and Dr. Fine noted.

Dr. Schuetz reported receiving support from BRAHMS Inc. Dr. Yealy reported conducting NIH-funded research in which Brahms AG provided biomarker assays. No other financial conflicts were noted. ■

Lung Cancer Deadlier in Women Treated With Hormone Therapy

BY JANE SALODOF MACNEIL
Elsevier Global Medical News

Hormone therapy in postmenopausal women increases the risk of death from lung cancer, according to a newly published post hoc analysis of the large and influential placebo-controlled Women's Health Initiative trial.

Lung cancer incidence was not higher in women who were treated with estrogen plus progesterone, but they were significantly more likely to die of the disease, the investigators reported. The mortality effect was most pronounced in smokers and former smokers. No difference was seen in mortality from small cell lung cancer.

Women who were treated with estrogen plus progesterone were more likely to die of lung cancer.

DR. CHLEBOWSKI

"Our findings should be considered before the initiation or continuation of combined hormone therapy in postmenopausal women, especially those with a high risk of lung cancer, such as current smokers or long-term past smokers," concluded the investigators, led by Dr. Rowan T. Chlebowski of Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, Calif. (Lancet 2009 Sept. 19 [doi:10.1016/S0140-6736(09)61526-9]).

The Women's Health Initiative trial randomized 16,608 mostly healthy postmenopausal women (8,506 to combined hormone therapy and 8,102 to placebo) at 40 centers in the United States from 1993 to 1998. It was halted after an average follow-up of 5.6 years when investigators determined that higher risks of cardiovascular disease, coronary heart disease, stroke, venous thromboembolism, and breast cancer outweighed the benefits from lower risks for fractures and colorectal cancers among women in the combined HT arm.

Lung cancer was not a predefined study outcome, but the investigators became suspicious when deaths from other cancers were not sufficient to explain excess mortality in women treated with HT.

The subsequent intent-to-treat analysis, performed at an average follow-up of 7.9 years, found that more lung cancer occurred in the combined HT arm (109 cases) than in women treated with placebo (85 cases), with non–small cell lung cancer (NSCLC) occurring in 96 and 72 women, respectively, in the two groups. These differences were not statistically significant, but the curves began to separate after 5 years, with more lung cancer (particularly NSCLC) occurring after that in women who were given combined HT than in those who had been on placebo.

Among the women who were diagnosed with lung cancer, 78 deaths occurred during follow-up in the combined HT arm vs. 49 in the placebo group, a difference that was statistically significant, with an incidence per year of 0.12% and 0.08%, respectively (hazard ratio, 1.50; $P = .03$), the investigators reported.

The Women's Health Initiative was supported by the National Heart, Blood, and Lung Institute of the National Institutes of Health. Dr. Chlebowski disclosed advisory and consulting relationships with various drug companies. ■

Indexes Help Make Admissions

Predictors • *from page 1*

in the Real World Registry) study, the first-ever large multicenter prospective observational study of pulmonary embolism in the United States.

The goal was to identify tools that will help emergency physicians decide whether to admit patients with pulmonary embolism to the ICU, a regular ward, or a telemetry bed, explained Dr. Kline, director of research in the department of emergency medicine at Carolinas Medical Center, Charlotte, N.C.

Five predictors were selected for study inclusion based upon the medical literature and widespread round-the-clock availability in U.S. EDs. The predictors were an oxygen saturation (SaO_2) below 95%, an abnormal serum troponin level, a brain natriuretic peptide level greater than 90 pg/mL or pro-brain natriuretic peptide level in excess of 900 pg/mL, a shock index greater than 1, and a PESI score greater than 100.

The shock index is obtained by dividing heart rate by systolic blood pressure. The PESI score, also known as the Aujesky prognostic model, was developed by a team led by Dr. Drahomir Aujesky of the University of Lausanne, Switzerland. It incorporates 11 simple patient factors shown to be independently associated with 30-day mortality in more than 15,000 pulmonary embolism patients.

Those factors include age greater than 65 years, male sex, and comorbid cancer, chronic pulmonary disease, or heart failure. Also, a systolic blood pressure less than 100 mm Hg, altered mental status, a respiratory rate of 30 per minute or more, heart rate of 110 bpm or more, temperature less than 36° C, and an SaO_2 of less than 90% (Am. J. Respir. Crit. Care Med. 2005;172:1041-6).

The composite in-hospital adverse outcome measure used in EMPEROR consisted of death from pulmonary embolism, shock requiring vasopressors, intubation, or surgical embolectomy. It occurred in 3.5% of patients. Nearly all adverse events happened within 48 hours; roughly two-thirds occurred within 24 hours.

Interestingly, Dr. Kline said, death from pulmonary embolism occurred in only 0.9% of EMPEROR participants. "That's in striking contrast to European data suggesting up to about 10% in-hospital mortality," he observed.

None of the predictors displayed good sensitivity for predicting adverse events. However, a PESI greater than 100 had outstanding specificity and conferred an 8.7-fold increased likelihood of adverse outcome. The shock index performed second best. The two vital signs proved to be slightly better predictors than the two biomarkers (see chart).

An upgrade to the ICU occurred in 1.5% of patients within 24 hours after their admission to a telemetry or regular hospital bed. "So, we do a pretty good job: 98.5% of our patients do not get an upgrade to an ICU," Dr. Kline noted.

Audience members said they are pressured by hospital administrators to identify patients with pulmonary embolism who can safely be discharged home. They asked whether any of the predictors were useful for that purpose.

Dr. Kline replied that he hasn't looked at the EMPEROR data toward that end. However, he is aware of ongoing European studies that suggest a PESI score lower than 50 or so shows potential for such a purpose.

EMPEROR was funded in part by GlaxoSmithKline. ■

How Prognostic Tools Stacked Up in EMPEROR

Predictor	Prevalence in patients with pulmonary embolism	Sensitivity	Specificity	Positive likelihood ratio
Shock index greater than 1	12%	33%	88%	2.9
PESI greater than 100	2%	17%	98%	8.7
SaO_2 below 95%	29%	58%	73%	2.1
Troponin	33%	48%	68%	1.5
Elevated brain natriuretic peptide	32%	37%	68%	1.1

Source: Dr. Kline

Elsevier Global Medical News

Maintenance Combo Delayed Lung Cancer Progression

BY PATRICE WENDLING
Elsevier Global Medical News

ORLANDO — Adding erlotinib to maintenance therapy with bevacizumab delayed disease progression in patients with advanced non–small cell lung cancer in the international phase IIIb ATLAS trial.

The median progression-free survival by investigator assessment was 4.76 months for bevacizumab (Avastin) plus erlotinib (Tarceva) and 3.75 months for bevacizumab plus placebo (hazard ratio, 0.72; $P = .0012$), Dr. Vincent Miller reported at the annual meeting of the American Society of Clinical Oncology. The 768-patient trial was stopped early after meeting this primary efficacy end point.

More patients receiving erlotinib were without disease progression at 3 months (68% vs. 53% of the placebo group) and at 6 months (40% vs. 28%). "I think to treating oncologists in the community, these numbers may have more impact than looking at a 1-month benchmark or that median time to progression," Dr. Miller told reporters during a press briefing on the study, which was sponsored by Genentech Inc.

Genentech and OSI Pharmaceuticals Inc. announced in March that they had applied to the Food and Drug Administration for approval of erlotinib as a first-line maintenance therapy in non–small cell lung cancer (NSCLC) patients whose disease had not progressed after first-line platinum-based chemotherapy. In addition, Roche (now the parent company of Genentech) applied for approval in Europe. The applications were based on data from the SATURN trial, another phase III placebo-controlled study presented at the ASCO meeting.

Dr. Miller reported that the benefit of adding erlotinib to bevacizumab was seen across multiple subgroups and, as in the SATURN trial, was most impressive among never smokers (hazard ratio, 0.34) and those of Asian or Pacific Islander ethnicity (HR, 0.16). There was a suggestion that patients with a history of treated brain metastases garner comparable benefit (HR, 0.44) compared with those with no brain metastases (HR, 0.69), although the 95% confidence interval (0.16-1.31)

More patients receiving erlotinib were without disease progression at 3 months and at 6 months.

DR. MILLER

does cross unity, said Dr. Miller, a thoracic oncologist with Memorial Sloan-Kettering Cancer Center in New York. No specific initial chemotherapy regimen suggested greater benefit with subsequent use of erlotinib.

Biomarker analyses and independent review of progression-free survival data are ongoing. Overall survival data were not mature at the time of the analysis, but are expected to be published later this year.

Study discussant Dr. Nasser Hanna of Indiana University in Indianapolis said he wanted to see the overall survival results from the ATLAS and SATURN trials. Meanwhile, he noted that there was no indication that patient quality of life or overall survival was improved with the maintenance therapy.

No new safety signals were observed in the trial, although there were incremental increases in adverse events with the addition of erlotinib to bevacizumab, Dr. Miller said.

Grade 3/4 events were reported in 162 (44%) of 367 patients in the erlotinib arm and in 112 (30%) of 368 in the placebo arm. The most common adverse events were rash and diarrhea.

In total, 768 patients were randomized to bevacizumab at a dose of 15 mg/kg plus 150 mg of erlotinib daily, or to bevacizumab plus placebo after four cycles of first-line chemotherapy with bevacizumab for locally advanced, recurrent, or metastatic non–small cell lung cancer. Their median age was 64 years, 52% were male, and 78% were white. About 85% had stage IV disease, 82% had adenocarcinoma histology, and 17% were never smokers.

Dr. Miller has been a consultant for, and has received honoraria from, Genentech Inc. His coauthors reported being on the speakers bureau for Genentech and Roche, or being employees of Genentech. ■

Chemotherapy Failed to Prolong Life in NATCH Trial

Chemotherapy toxicity was not significantly more pronounced in the preoperative group.

BY BETSY BATES
Elsevier Global Medical News

SAN FRANCISCO — An ambitious European trial failed to show any significant differences in overall survival among early-stage lung cancer patients randomized to receive either surgery alone or surgery in combination with preoperative or adjunctive chemotherapy.

Results of the much-awaited NATCH (Neoadjuvant or Adjuvant Chemotherapy in Patients With Operable Non–Small Cell Lung Cancer) trial were presented at the World Conference on Lung Cancer.

In all, 624 patients with clinical stage IA (tumor larger than 2 cm), IB, II, or T3N1 non–small cell lung cancer were randomized to receive surgery alone (212 patients), preoperative chemotherapy followed by surgery (201 patients), or surgery followed by adjunctive chemotherapy (211 patients).

Patients receiving chemotherapy before surgery were far more likely to receive the full three-cycle regimen of paclitaxel and carboplatin that was called for in the study design than were those who underwent surgery first (97% vs. 66% of patients, respectively).

Preoperative chemotherapy did not significantly interfere with patients' ability to undergo surgery, which went forward as planned in 91% of patients assigned to that treatment, compared with 96% in the adjunctive treatment arm and 95% assigned to receive surgery alone.

Chemotherapy toxicity was not significantly more pronounced in the preoperative group, with fewer than 10% of patients in either chemotherapy arm experiencing grade 3 neutropenia, the most common serious adverse event.

A radiologic response was achieved in 106 (53%) of the patients who were pretreated with chemotherapy, including pathologic complete response in 19 (9.5%).

Yet, despite all these seemingly positive signs, preoperative chemotherapy was associated with only an insignificant trend in favor of improved median overall survival (55.2 weeks, compared with 50.3 weeks for those who received adjunctive chemotherapy and 48.8 weeks for those who received surgery alone).

At 3 years, the survival rates were 59.2%, 58.4%, and 58.6% among patients receiving preoperative and adjunctive chemotherapy, and surgery alone, reported Dr. Enriqueta Felip of Vall d'Hebron University Hospital in Barcelona, who presented the study on behalf of the Spanish Lung Cancer Group.

A subgroup analysis provided a hint of chemotherapeutic benefit for patients with stage II/T3N1 disease, Dr. Felip said at the meeting, which was sponsored by the International Association for the Study of Lung Cancer.

Although the study was not powered to show a significant difference by stage, those with at least stage II disease who received preoperative chemotherapy were more likely than were surgery-alone patients to achieve 5 years of disease-free survival (36.6% vs. 25%; hazard ratio, 0.81; range, 0.64-1.02). The adjunctive chemotherapy group showed a similar trend, with a 5-year disease-free survival rate of 31% (HR, 0.87; range, 0.54-1.38).

PREOPERATIVE CHEMOTHERAPY WAS ASSOCIATED WITH ONLY AN INSIGNIFICANT TREND IN FAVOR OF IMPROVED MEDIAN OVERALL SURVIVAL.

Those results were "tantalizingly close to significance," and warrant closer scrutiny, said Dr. David Jablons, FCCP, chief of thoracic surgery at the University of California, San Francisco, a formal discussant of the paper.

"We were all very excited at the start of this race, and tried to figure out which horse to bet on," Dr. Jablons said during the presidential symposium at the meeting. "I will tell you that the bias in our camp, in northern California, was on the preoperative [chemotherapy] horse. However, the data remains what it is."

The failure to reach statistical significance may have been related to the inclusion of clinical stage I and node-negative patients in the 7-year trial, who today are not generally believed to benefit from nondirected chemotherapy, he added.

Dr. Peter Goldstraw of Royal Brompton Hospital in London later commented on the study during a press conference on multimodality treatment for lung cancer.

"It doesn't show that chemotherapy doesn't work," he said. "I think what it shows is that we've got to be very, very selective."

Improved staging technologies and patient selection by molecular analysis will help to achieve that goal, noted Dr. Jablons.

Dr. Felip reported that she had no financial disclosures. ■

Dr. W. Michael Alberts, FCCP, comments: *This study calls into question the use of adjuvant or neoadjuvant chemotherapy in patients with completely resectable lung cancer (stage I and II). As mentioned, the study was not powered, however, to show a significant difference by stage. Therefore, this study is unlikely to change the current recommendation to use adjuvant chemotherapy in patients with stage II disease.*

Rash May Predict Benefit of Cetuximab in Lung Cancer

BY PATRICE WENDLING
Elsevier Global Medical News

ORLANDO — KRAS mutation status and epidermal growth factor receptor gene copy number do not predict improved benefit from the addition of cetuximab to first-line chemotherapy in non–small cell lung cancer.

Instead, rash appears to be the best predictor of clinical benefit with cetuximab (Erbitux), according to a biomarker analysis of the multinational phase III FLEX (First-Line Erbitux in Lung Cancer) trial.

The finding is striking because KRAS mutation status has been shown to predict cetuximab benefit in colorectal cancer. This practice-changing discovery was identified by the American Society of Clinical Oncology as one of the top research advances in 2008, and KRAS testing has since been incorporated into practice guidelines in the United States and Europe.

In the current analysis, archived tumor samples from 35% of the 1,125 FLEX patients were evaluated, and a KRAS mutation was detected in 75 of 395 (19%) samples. There was no significant difference in overall survival by KRAS mutation status or by treatment type, Dr. Kenneth J. O'Byrne of St. James Hospital in Dublin reported at ASCO's annual meeting.

Among patients with wild-type KRAS tumors, median overall survival was 11.4 months with chemotherapy plus cetuximab vs. 10.3 months with chemotherapy alone (hazard ratio, 0.96). In those with KRAS mutant tumors, median overall survival was 8.9 months in the cetuximab arm vs. 11.1 months in the control arm (HR, 1.00).

Progression-free survival and response rates were also not significantly different based on KRAS mutation status or treatment type, Dr. O'Byrne said.

Epidermal growth factor receptor (EGFR) gene copy number analysis by fluorescent in-situ hybridization (FISH) assay showed that 37% of patients in the cetuximab arm and 36% in the control arm were FISH positive based on the University of Colorado Cancer Center scoring system. In this system, tumors with at least 40% of cells displaying at least four copies of EGFR signals or with EGFR gene amplification are classified as EGFR FISH positive (Diagn. Pathol. 2006;1:19).

Among FISH-negative patients, median overall survival was 10.6 months with chemotherapy plus cetuximab vs. 10.0 months with chemotherapy alone (HR, 0.91). In FISH-positive patients, median overall survival was 11.6 months in the cetuximab arm vs. 9.9 months in the control arm (HR, 0.85).

Similarly, progression-free survival and response rates by FISH status failed to indicate response to cetuximab therapy.

"I think there's much work to do with biomarkers in the future," Dr. O'Byrne said. "It would be wonderful to identify them with a specific test, but we just aren't there yet."

He said that one of the most important findings of the analysis was that first-cycle rash can help identify patients with increased survival with cetuximab.

Median overall survival was 15.0 months in patients who developed an acnelike rash of any grade within 21 days of treatment with cetuximab and chemotherapy vs. 8.8 months for those without a rash after cetuximab treatment (HR, 0.63; *P* less than .001). In contrast, survival was 10.3 months in the chemotherapy-alone arm.

Median overall survival was 15.0 months in 290 patients with a grade 1-3 rash and 14.7 months in 120 patients with a grade 2-3 rash, indicating that the development of a rash is what's important, rather than the specific grade of the rash, Dr. O'Byrne said.

Overall, the findings suggest that the optimal selection strategy for treatment with cetuximab remains to be defined, and they raise an intriguing prospect for physicians, Dr. George R. Simon said during a discussion of the study.

"This was brought up by someone in the audience and is worth thinking about in my opinion: If patients with cetuximab do not get a rash for the first cycle, is it worth continuing cetuximab?" he asked.

The FLEX trial KRAS and EGFR-biomarker data are congruent with those from the smaller BMS-099 trial, in which cetuximab was added to a taxane and carboplatin in the first-line treatment of NSCLC, observed Dr. Simon, director of thoracic oncology at Fox Chase Cancer Center in Philadelphia.

Previous data from FLEX showed a statistically significant survival benefit for the addition of cetuximab to cisplatin- and vinorelbine-based chemotherapy in stage wet IIIB or stage IV NSCLC, regardless of histology (Lancet 2009;373:1525-31).

The FLEX trial was conducted by Merck KGaA in Darmstadt, Germany. The investigators revealed employment with Merck KGaA, consultancy with Merck, honoraria from Merck KGaA, Merck & Co., Roche, Pierre Fabre Pharmaceuticals Inc., and Eli Lilly & Co., and research funding from Merck and Merck KGaA. ■

Post-TBI Sleep-Wake Disturbances Go Undetected

BY SUSAN LONDON
Elsevier Global Medical News

SEATTLE — Roughly half of patients who have experienced a traumatic brain injury develop a sleep-wake disturbance as a result, but these disturbances are often not recognized by patients or physicians, Dr. Christian R. Baumann said at the annual meeting of the Associated Professional Sleep Societies.

Although the situation is improving, the general public has been slow to recognize a link between traumatic brain injury (TBI) and sleep perturbations, said Dr. Baumann, a neurologist at the University Hospital Zurich. Fewer than 30 systematic studies on this topic have been published, most of them in low-impact journals.

Several factors explain why post-TBI sleep-wake disturbances are under-represented in the medical literature, he commented, including the use in studies of inadequate methodology, reliance on unvalidated assessment tools, selection bias because many studies have been performed in rehabilitation centers, and the often retrospective nature of the studies.

In a prospective study that Dr. Baumann and his colleagues conducted among a cohort of 65 consecutive patients in Zurich who experienced TBI, the injury as assessed 1-4 days afterward was classified as mild in 40% of patients, moderate in 23%, and severe in 37% (Brain 2007;130:1873-83).

"Six months later, the general outcome was good—better than we expected and better than the literature says," he commented, with 48% of patients having a good clinical recovery, 46% having moderate disability, and only 6% having severe disability.

However, a variety of sleep assessments showed that 72% of the patients had at least one sleep-wake disturbance at that time. By type, 38% had excessive daytime sleepiness, 22% had hypersomnia (slept at least 2 hours more daily than before their injury), 17% had fatigue, and 5% had insomnia. None had circadian sleep disorder.

"We looked for other reasons for the sleep disturbances," he said, such as sleep apnea. But in 60% of affected patients (comprising 43% of the cohort), no etiology other than the trauma itself could be identified. Further analyses showed that the occurrence of the disturbances was independent of the anatomic location of injury, the severity of the trauma, age, sex, and extent of recovery.

Discussing similar research, Dr. Baumann noted that excessive daytime sleepiness has consistently been a common finding after TBI, occurring in 25%-46% of patients, although there was a lack of studies of its treatment in this context. A small randomized study of 53 participants with TBI found that treatment with modafinil was ineffective (J. Head Trauma Rehabil. 2008;23:52-63).

Fatigue is more difficult to assess because there are no objective measures of fatigue, he noted. But post-TBI fatigue has been reported in up to a third of patients, and in one study was correlated with both excessive daytime sleepiness and impaired driving ability (Neurology 2008;71:1609-13).

"One of the conclusions of this paper was that there may be a continuum between fatigue and excessive daytime sleepiness, at least in TBI patients," he added. And 3-year data from the Zurich cohort appear to support this conclusion, showing a decrease in the prevalence of subjective excessive daytime sleepiness from that seen at 6 months but an increase in the prevalence of fatigue. "So it is possible that there is some shift from excessive daytime sleepiness to fatigue," he said.

Estimates of insomnia after TBI have ranged widely, from 5% to 80%, with some evidence suggesting that this condition may be more common when subjectively versus objectively rated (Sleep Med. 2006;7:486-97). The reported prevalence of circadian sleep disorders after TBI has ranged from 0% to 36%.

Many patients with post-TBI sleep disturbances do not seek help for them or do not report them during medical visits, according to Dr. Baumann. "My primary explanation is that patients underestimate their sleep-wake disturbances," he said. In addition, the Zurich cohort at least was mainly male, and men may fail to report the disturbances because they are stoic and worry about driving restrictions and such.

Follow-up of patients after TBI is

therefore important, he asserted. "We routinely see these patients 6 months after their injury. Otherwise, we would miss them," he said. Furthermore, physicians should maintain a high index of suspicion for sleep-wake disturbances in this population. "If you really question patients after TBI [about symptoms], then you will find more."

As far as the possible etiology of post-TBI sleep-wake disturbances, evidence has implicated a reduction in levels of hypocretin (orexin), a neurotransmitter produced by cells in the posterolateral hypothalamus that promotes wakefulness. "These cells have excitatory connections to many monoaminergic and cholinergic cell groups that promote arousal," he pointed out.

Compared with healthy controls and with patients with most other neurologic disorders and sleep disorders, patients in the Zurich cohort with TBI had lower cerebrospinal fluid (CSF) levels of hypocretin at 1-4 days after injury, with some even had undetectable levels, Dr. Baumann reported. But their levels were comparable to those in patients having narcolepsy, suggesting the conditions may have a similar underlying mechanism.

Repeated measurement of CSF hypocretin levels at 6 months in the TBI group showed that levels had increased from those seen acutely in the majority of patients and were now normal in many cases.

Still, a small proportion of patients had persistently low levels, and low levels were correlated with excessive daytime sleepiness.

In a related study, he and his colleagues found that the number of hypocretin-positive hypothalamic cells was 30% lower in patients who died after TBI than in people who died from other causes.

"We hypothesize that a loss of hypocretin cells, which may recover to a certain extent, may account in part for excessive daytime sleepiness and hypersomnia after TBI," he said, but added that research on the pathophysiology is still in its infancy.

"It's really important that we do have systematic studies on post-TBI sleep-wake disturbances to better characterize them, to define their causes, and also to enable effective treatment."

Dr. Baumann reported that he had no conflicts of interest in association with his presentation. ■

ADCIRCA™ (tadalafil) Tablets

BRIEF SUMMARY

The following is a brief summary of the full prescribing information on ADCIRCA (tadalafil). Please review the full prescribing information prior to prescribing ADCIRCA.

INDICATIONS AND USAGE

Pulmonary Arterial Hypertension

ADCIRCA is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability.

CONTRAINDICATIONS

Concomitant Organic Nitrates

Do not use ADCIRCA in patients who are using any form of organic nitrate, either regularly or intermittently. ADCIRCA potentiates the hypotensive effect of nitrates. This potentiation is thought to result from the combined effects of nitrates and ADCIRCA on the nitric oxide/cGMP pathway.

Hypersensitivity Reactions

ADCIRCA is contraindicated in patients with a known serious hypersensitivity to tadalafil (ADCIRCA or CIALIS). Hypersensitivity reactions have been reported, including Stevens-Johnson syndrome and exfoliative dermatitis.

WARNINGS AND PRECAUTIONS

Cardiovascular Effects

Discuss with patients the appropriate action to take in the event that they experience anginal chest pain requiring nitroglycerin following intake of ADCIRCA. At least 48 hours should elapse after the last dose of ADCIRCA before taking nitrates. If a patient has taken ADCIRCA within 48 hours, administer nitrates under close medical supervision with appropriate hemodynamic monitoring. Patients who experience anginal chest pain after taking ADCIRCA should seek immediate medical attention.

PDE5 inhibitors, including tadalafil, have mild systemic vasodilatory properties that may result in transient decreases in blood pressure. Prior to prescribing ADCIRCA, carefully consider whether patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects. Patients with severely impaired autonomic control of blood pressure or with left ventricular outflow obstruction, (e.g., aortic stenosis and idiopathic hypertrophic subaortic stenosis) may be particularly sensitive to the actions of vasodilators, including PDE5 inhibitors.

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

There is a lack of data on safety and efficacy in the following groups who were specifically excluded from the PAH clinical trials:

- Patients with clinically significant aortic and mitral valve disease
- Patients with pericardial constriction
- Patients with restrictive or congestive cardiomyopathy
- Patients with significant left ventricular dysfunction
- Patients with life-threatening arrhythmias
- Patients with symptomatic coronary artery disease
- Patients with hypotension (<90/50 mm Hg) or uncontrolled hypertension

Use with Alpha Blockers and Antihypertensives

PDE5 inhibitors, including ADCIRCA, and alpha–adrenergic blocking agents are vasodilators with blood pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes can lower blood pressure significantly, which may lead to symptomatic hypotension (e.g., fainting). Safety of combined use of PDE5 inhibitors and alpha blockers may be affected by other variables, including intravascular volume depletion and use of other antihypertensive drugs.

Use with Alcohol

Both alcohol and tadalafil are mild vasodilators. When mild vasodilators are taken in combination, blood pressure-lowering effects are increased.

Use with Potent CYP3A Inhibitors or Inducers

Co-administration of ADCIRCA in Patients on Ritonavir

In patients receiving ritonavir for at least one week, start ADCIRCA at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.

Co-administration of Ritonavir in Patients on ADCIRCA

Avoid use of ADCIRCA during the initiation of ritonavir. Stop ADCIRCA at least 24 hours prior to starting ritonavir. After at least one week following the initiation of ritonavir, resume ADCIRCA at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.

Other Potent Inhibitors of CYP3A

Tadalafil is metabolized predominantly by CYP3A in the liver. In patients taking potent inhibitors of CYP3A such as ketoconazole and itraconazole, avoid use of ADCIRCA.

Potent Inducers of CYP3A

For patients chronically taking potent inducers of CYP3A, such as rifampin, avoid use of ADCIRCA.

Use in Renal Impairment

In patients with mild or moderate renal impairment

Start dosing at 20 mg once daily. Increase the dose to 40 mg once daily based upon individual tolerability.

In patients with severe renal impairment

Avoid use of ADCIRCA because of increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis.

Use in Hepatic Impairment

In patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A and B)

Because of limited clinical experience in patients with mild to moderate hepatic cirrhosis, consider a starting dose of 20 mg once daily ADCIRCA.

In patients with severe hepatic cirrhosis (Child-Pugh Class C)

Patients with severe hepatic cirrhosis have not been studied. Avoid use of ADCIRCA.

Effects on the Eye

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

Patients with known hereditary degenerative retinal disorders, including retinitis pigmentosa, were not included in the clinical trials, and use in these patients is not recommended.

Hearing Impairment

Physicians should advise patients to seek immediate medical attention in the event of sudden decrease or loss of hearing. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including ADCIRCA. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors.

Combination with Other PDE5 Inhibitors

Tadalafil is also marketed as CIALIS. The safety and efficacy of taking ADCIRCA together with CIALIS or other PDE5 inhibitors have not been studied. Inform patients taking ADCIRCA not to take CIALIS or other PDE5 inhibitors.

Prolonged Erection

There have been rare reports of prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) for this class of compounds. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Patients who have an erection lasting greater than 4 hours, whether painful or not, should seek emergency medical attention.

ADCIRCA should be used with caution in patients who have conditions that might predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia), or in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis, or Peyronie's disease).

Effects on Bleeding

PDE5 is found in platelets. When administered in combination with aspirin, tadalafil 20 mg did not prolong bleeding time, relative to aspirin alone. ADCIRCA has not been administered to patients with bleeding disorders or significant active peptic ulceration. Although ADCIRCA has not been shown to increase bleeding times in healthy subjects, use in patients with bleeding disorders or significant active peptic ulceration should be based upon a careful risk-benefit assessment.

ADVERSE REACTIONS

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

• Hypotension • Vision loss • Hearing loss • Priapism

Clinical Trials Experience

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

Tadalafil was administered to 398 patients with PAH during clinical trials worldwide. In trials of ADCIRCA, a total of 311 and 251 subjects have been treated for at least 182 days and 360 days, respectively. The overall rates of discontinuation because of an adverse event (AE) in the placebo-controlled trial were 9% for ADCIRCA 40 mg and 15% for placebo. The rates of discontinuation because of AEs, other than those related to worsening of PAH, in patients treated with ADCIRCA 40 mg was 4% compared to 5% in placebo-treated patients.

In the placebo-controlled study, the most common AEs were generally transient and mild to moderate in intensity. Table 1 presents treatment-emergent adverse events reported by ≥ 9% of patients in the ADCIRCA 40 mg group and occurring more frequently than with placebo.

TABLE 1: Treatment-Emergent Adverse Events Reported by ≥ 9% of Patients in ADCIRCA and More Frequent than Placebo by 2%

EVENT	Placebo (%) (N=82)	ADCIRCA 20 mg (%) (N=82)	ADCIRCA 40 mg (%) (N=79)
Headache	15	32	42
Myalgia	4	9	14
Nasopharyngitis	7	2	13
Flushing	2	6	13
Respiratory Tract Infection (Upper and Lower)	6	7	13

TABLE 1: Treatment-Emergent Adverse Events Reported by ≥ 9% of Patients in ADCIRCA and More Frequent than Placebo by 2% (cont)

EVENT	Placebo (%) (N=82)	ADCIRCA 20 mg (%) (N=82)	ADCIRCA 40 mg (%) (N=79)
Pain in Extremity	2	5	11
Nausea	6	10	11
Back Pain	6	12	10
Dyspepsia	2	13	10
Nasal Congestion (Including sinus congestion)	1	0	9

Postmarketing Experience

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

Cardiovascular and cerebrovascular — Serious cardiovascular events, including myocardial infarction, sudden cardiac death, stroke, chest pain, palpitations, and tachycardia, have been reported postmarketing in temporal association with the use of tadalafil. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of tadalafil without sexual activity. Others were reported to have occurred hours to days after the use of tadalafil and sexual activity. It is not possible to determine whether these events are related directly to tadalafil, to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors.

Body as a whole — Hypersensitivity reactions including urticaria, Stevens–Johnson syndrome, and exfoliative dermatitis

Nervous — Migraine, seizure and seizure recurrence, and transient global amnesia

Ophthalmologic — Visual field defect, retinal vein occlusion, and retinal artery occlusion

Non–arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely postmarketing in temporal association with the use of PDE5 inhibitors, including tadalafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for development of NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia, and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors.

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

Urogenital — Priapism.

DRUG INTERACTIONS

Potential for Pharmacodynamic Interactions with ADCIRCA

Nitrates

Do not use ADCIRCA in patients who are using any form of organic nitrate. In clinical pharmacology studies ADCIRCA potentiated the hypotensive effect of nitrates. In a patient who has taken ADCIRCA, where nitrate administration is deemed medically necessary in a life–threatening situation, at least 48 hours should elapse after the last dose of ADCIRCA before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring.

Alpha-Blockers

PDE5 inhibitors, including ADCIRCA, and alpha–adrenergic blocking agents are both vasodilators with blood-pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. Clinical pharmacology studies have been conducted with coadministration of tadalafil with doxazosin, alfuzosin or tamsulosin.

Antihypertensives

PDE5 inhibitors, including ADCIRCA, are mild systemic vasodilators. Clinical pharmacology studies were conducted to assess the effect of tadalafil on the potentiation of the blood–pressure–lowering effects of selected antihypertensive medications (amlodipine, angiotensin II receptor blockers, bendroflumethiazide, enalapril, and metoprolol). Small reductions in blood pressure occurred following coadministration of tadalafil with these agents compared with placebo.

Alcohol

Both alcohol and tadalafil, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood pressure–lowering effects of each individual compound may be increased. Substantial consumption of alcohol (e.g., 5 units or greater) in combination with ADCIRCA can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache. Tadalafil (10 mg or 20 mg) did not affect alcohol plasma concentrations and alcohol did not affect tadalafil plasma concentrations.

Potential for Other Drugs to Affect ADCIRCA

Ritonavir

Ritonavir initially inhibits and later induces CYP3A, the enzyme involved in the metabolism of tadalafil. At steady state of ritonavir (about 1 week), the exposure to tadalafil is similar as in the absence of ritonavir.

Other Potent Inhibitors of CYP3A

Tadalafil is metabolized predominantly by CYP3A in the liver. In patients taking potent inhibitors of CYP3A such as ketoconazole, and itraconazole, avoid use of ADCIRCA.

Potent Inducers of CYP3A

For patients chronically taking potent inducers of CYP3A, such as rifampin, avoid use of ADCIRCA.

Potential for ADCIRCA to Affect Other Drugs

Cytochrome P450 Substrates

Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolized by cytochrome P450 (CYP) isoforms (e.g., theophylline, warfarin, midazolam, lovastatin, bosentan).

Aspirin

Tadalafil (10 mg and 20 mg once daily) does not potentiate the increase in bleeding time caused by aspirin.

P-glycoprotein *(e.g., digoxin)*

Coadministration of tadalafil (40 mg once daily) for 10 days did not significantly alter digoxin pharmacokinetics in healthy subjects.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

Animal reproduction studies in rats and mice revealed no evidence of fetal harm. There are, however, no adequate and well-controlled studies of tadalafil in pregnant women. Because animal reproduction studies are not always predictive of human response, tadalafil should be used during pregnancy only if clearly needed.

Non–teratogenic effects

Animal reproduction studies showed no evidence of teratogenicity, embryotoxicity, or fetotoxicity when tadalafil was given to pregnant rats or mice at unbound tadalafil exposures up to 7 times the maximum recommended human dose (MRHD) of 40 mg/day during organogenesis. In one of two perinatal/postnatal developmental studies in rats, postnatal pup survival decreased following maternal exposure to unbound tadalafil concentrations greater than 5 times the MRHD based on AUC. Signs of maternal toxicity occurred at doses greater than 8 times the MRHD based on AUC. Surviving offspring had normal development and reproductive performance.

Nursing Mothers

It is not known whether tadalafil is excreted into human milk. While tadalafil or some metabolite of tadalafil was excreted into rat milk, drug levels in animal breast milk may not accurately predict levels of drug in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when ADCIRCA is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of ADCIRCA in pediatric patients have not been established.

Geriatric Use

Of the total number of subjects in the clinical study of tadalafil for pulmonary arterial hypertension, 28 percent were 65 and over, while 8 percent were 75 and over. No overall differences in safety were observed between subjects over 65 years of age compared to younger subjects or those over 75 years of age. No dose adjustment is warranted based on age alone; however, a greater sensitivity to medications in some older individuals should be considered.

Renal Impairment

For patients with mild or moderate renal impairment, start ADCIRCA at 20 mg once daily. Increase the dose to 40 mg once daily based upon individual tolerability.

In patients with severe renal impairment, avoid use of ADCIRCA because of increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis.

Hepatic Impairment

Because of limited clinical experience in patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A or B), consider a starting dose of ADCIRCA 20 mg once daily. Patients with severe hepatic cirrhosis (Child-Pugh Class C) have not been studied, thus avoid use of ADCIRCA in such patients.

OVERDOSAGE

Single doses up to 500 mg have been given to healthy male subjects, and multiple daily doses up to 100 mg have been given to male patients with erectile dysfunction. Adverse reactions were similar to those seen at lower doses. Doses greater than 40 mg have not been studied in patients with pulmonary arterial hypertension. In cases of overdose, standard supportive measures should be adopted as needed. Hemodialysis contributes negligibly to tadalafil elimination.

Marketed by United Therapeutics Corporation, Research Triangle Park, NC 27709

Rx only June 2009

www.adcirca.com

Pulmonary Perspectives

Gain New "Perspectives" in Pulmonary Medicine at CHEST 2009

San Diego is the place to be October 31 to November 5 for the annual CHEST meeting of the ACCP. A pulmonary track can be followed throughout the many activities planned during the meeting. From the more than 300 sessions, to special presentations in the Clinical Resource Center (formerly the exhibit hall), to simulation education and clinical case puzzlers, to literature reviews and the PCCU lessons in the Self-study Clinical Library, or NetWork Highlights, you are sure to gain lots of new "pulmonary perspectives." Here is a small sample of things you will not want to miss:

SESSIONS BY CURRICULUM

Allergy and Airway

Monday, November 2
8:00 AM - 9:15 AM
Airways Disorders NetWork: Safety of COPD Medications
Update on CF for Adult and Pediatric Pulmonologists

10:30 AM - 12:00 PM
Exacerbations of Chronic Respiratory Disease: State of the Art
The Legacy of Pediatric Lung Disease

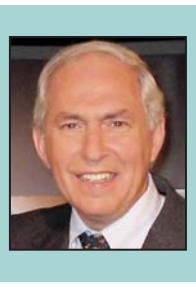
2:30 PM - 3:30 PM
CTS Institute of Circulatory and Respiratory Health Distinguished Lecture in the Respiratory Sciences—Airway Remodeling in Asthma: Implications for Disease Severity

Tuesday, November 3
6:00 AM - 7:30 AM
Lessons in Asthma Management: Optimizing Management Strategies

10:30 AM - 12:00 PM
American Academy of Allergy, Asthma, and Immunology: Allergy Symposium
Update on COPD Clinical Trials

4:30 PM - 6:00 PM
Management of the Difficult Airway

Wednesday, November 4
3:30 PM - 5:00 PM
Asthma Education: How Well Does It Work?
Comorbidities in COPD: An Interactive Session



Dr. Gene L. Colice, FCCP
Editor,
Pulmonary Perspectives

Thursday, November 5
9:45 AM - 11:15 AM
Say It Softly: The Hoarse Voice and the Pulmonologist

Chest Infections

Monday, November 2
10:30 AM - 12:00 PM
Community-Acquired Pneumonia: Severity Scoring

2:30 PM - 3:30 PM
Influenza Update: Vaccine Development to Pandemic Preparedness

CHEST 2009
October 31 - November 5
San Diego, California

Tuesday, November 3
8:00 AM - 9:15 AM
Chest Infections NetWork: Fungal Lung Disease in the Immunocompromised Host

2:30 PM - 3:30 PM
TB and Other Mycobacterial Diseases: Diagnosis and Monitoring

4:30 PM - 6:00 PM
Literature Review: COPD, Asthma, and Chest Infections

Wednesday, November 4
8:00 AM - 9:15 AM
Late-Breaking Abstracts
Lung Transplantation Is Not Appropriate for All Patients With Advanced CF

10:30 AM - 12:00 PM
Bronchiectasis: What's New in the Therapeutic Pipeline?
Ongoing Clinical Trials in Sepsis, Mechanical Ventilation, and Ventilator-Associated Pneumonia

3:30 PM - 5:00 PM
Controversies in the Management of Adult Respiratory Infections

Thursday, November 5
8:00 AM - 9:30 AM
Challenges of TB in the 21st Century: The World Must Work Together

9:45 AM - 11:15 AM
Community-Acquired Pneumonia and Real-Life Cases: What To Do When the Guidelines Don't Fit the Patient

Interventional Pulmonology

Monday, November 2
8:00 AM - 9:15 AM
Pasquale Ciaglia Memorial Lecture in Interventional Medicine

Tuesday, November 3
8:00 AM - 9:15 AM
Approach to Patients With a Pleural Effusion

Wednesday, November 4
10:30 AM - 12:00 PM
What Is the Best Modality To Sample the Peripheral Lung Nodule?

12:45 PM - 2:00 PM
Advanced Bronchoscopic Techniques Posters

Thursday, November 5
8:00 AM - 9:30 AM
Introduction of New Interventional and Diagnostic Technologies to the Pulmonary Practice

Pulmonary Vascular Disease

Monday, November 2
6:00 AM - 7:30 AM
Ongoing Clinical Trials in Interstitial Lung Disease, Pulmonary Hypertension, and COPD
What's New in Pulmonary Arterial Hypertension? Update on the 4th World Symposium on Pulmonary Hypertension

2:30 PM - 3:30 PM
Prophylaxis for Venous Thromboembolism in Hospitalized Patients

4:30 PM - 6:00 PM
Chronic Thromboembolic Disease: Essentials for the Busy Pulmonary/Critical Care Physician

Tuesday, November 3
6:00 AM - 7:30 AM
Case Studies in Pulmonary Vascular Disease: What Every Pulmonologist Should Know

8:00 AM - 9:15 AM
Management of Massive and Submassive Pulmonary Embolism

4:30 PM - 6:00 PM
Vexing Vessels

Wednesday, November 4
8:00 AM - 9:15 AM
Pulmonary Vascular Disease NetWork: A Superior Method of Oral Anticoagulation Management To Substantially Reduce Event Rates, Improve Quality of Life, and Reduce Health-care Costs

10:30 AM - 12:00 PM
The Management and Implementation of Anticoagulation Requirements

Thursday, November 5
8:00 AM - 9:30 AM
Acute Pulmonary Embolism: Treatment and Outcomes
Pulmonary Complications of Sickle Cell Disease in Children and Adults

9:45 AM - 11:15 AM
Controversies in Pulmonary Hypertension: Exercise-Induced? Borderline Disease?
Sleep and Pulmonary Hypertension: A Pro/Con Debate

Plus - Daily presentations in the curriculum areas of Diffuse Lung Disease, Disorders of the Pleura, Lung Cancer, Lung Pathology, Obstructive Lung Diseases, and others.

And – Clinical Case Puzzlers

Monday, November 2
10:30 AM - 12:00 PM – Intrathoracic Malignancies
4:30 PM - 6:00 PM – Lung Nodules

Tuesday, November 3
10:30 AM - 12:00 PM – Diffuse Lung Disease
4:30 PM - 6:00 PM – Pleural Diseases

Wednesday, November 4
10:30 AM - 12:00 PM – Pulmonary Vascular Disease
3:30 PM - 5:00 PM – Airways Disease

And – Self-Study Clinical Library

Earn CME
Sample PCCU Topics:
► Asthma Treatment: Step-Down and As-Needed Use of Inhaled Corticosteroids
► World Health Organization Groups II and III Pulmonary Hypertension: When and How To Treat
► An Introduction to Pleural Ultrasonography for the Pulmonary and Critical Care Physician
► The Pathophysiology and Treatment of Dyspnea
► Evaluation of the Patient with a Pleural Effusion
Sample Mini-Sessions:
► The Multidisciplinary Diagnosis of Diffuse Parenchymal Lung Disease
► Latent TB Infection: Why Don't We Practice What We Teach?

And – Presentations in Experience ACCP

► Lung Cancer and Antithrombotic Clinical Resources
► Coding Pulmonary Office Procedures
► Distinguished Scholar in Respiratory Health—COPD

Editor's Insight

I am always amazed at how varied and current the clinical offerings are at the annual CHEST meeting. For either the practicing pulmonologist or the academician, the tremendous amount of information provided on pulmonary and critical care medicine is well worth the trip.

BY DR. JAMES A. L. MATHERS, JR., FCCP

PRESIDENT'S REPORT

ACCP Celebrates '75 Years of Inspiration'

As I write this article, the summer of 2009 is almost over; members of the ACCP leadership are preparing to leave for the annual meeting of the European Respiratory Society, where some of us will be lecturing; and the time for CHEST 2009 is rapidly approaching.

The ACCP will celebrate "75 Years of Inspiration" during CHEST 2009. While we have had successful educational offerings this past year, under the guidance of Ed Dellert, RN, MBA, Vice President of Educational Resources, and our Education Committee, the ACCP is defined by the annual meeting, from the honors awarded for leadership and mentoring in the field of chest medicine to cutting-edge presentations by thought leaders.

While the meeting's foundation is planted in established clinical science, you will find a clear vision of evolving technology. I am looking forward to the many events and educational opportunities that have been combined into a unique program. This year's program—designed by COL Lisa K. Moores, MC, USA, FCCP, Program Chair; the ACCP NetWorks; and the CHEST Executive Committee—will include an exploration of the potential of telecommunication to improve patient-focused care.

Technology has dramatically changed our clinical practice during my career. Research-based pharmaceutical companies have developed medications that have significantly improved the quality of life for my patients. Advances in electrical and mechanical engineering have provided us with new tools for diagnosis and therapeutic intervention. As I left my fellowship, CTs were unheard of in clinical practice, and the treatment for the newly recognized sleep apnea was tracheotomy. We face a new horizon in communications technology that has the promise to improve the quality of patient care while making our clinical practice more organized, seamless, and effective.

For example, COPD is one of our "bread and butter" diseases. It is common, relatively easy to diagnose, and there are readily available practice guidelines for the management of these patients, yet there are 2 million yearly unplanned ED visits for exacerbation of this disease. Several studies document that these patients have progressive symptoms 3 to 5 days before arriving in the ED, and this is echoed by my personal experience. I would much rather see these patients in my office early in the course of their exacerbation than in the ED in the middle of the night.

Literature on vertically integrated systems, such as those in Great Britain and the European Union, has documented the ability of telemonitoring and telemedicine to reduce unplanned ED visits and hospitalizations, as well as shorten hospital stays. These health-care systems, with incentives to reduce costly ED visits and hospitalizations, are now aggressively implementing such programs for management of chronic diseases, such as COPD, heart failure, and diabetes.

The US Department of Defense has established the Telemedicine and Advanced Technology Research Center in Fort Detrick, MD. The Department of Veterans Affairs has begun to explore the use of this technology for patient-focused care. The goal of telemonitoring is timely communication of clinically meaningful and actionable information, while telemedicine can help deliver crucial therapies quickly.

I urge you to attend the CHEST 2009 keynote address by Dr. Jay H. Sanders, a pioneer in the field of telemedicine, who has had a fascinating national and international career. COL Ron K. Poropatich, MC, USA, FCCP, a leader in telehealth research and implementation for the DOD, will speak about the use

of telemedicine in home care. Dr. Craig M. Lilly, FCCP, who has been a leader in using telemedicine in the care of the critically ill and injured, will direct several practical sessions on intensive care unit telemedicine.

If you are interested in reducing disparities in health care, I recommend attending the Cultural Diversity Luncheon, where the speaker will be Bonnie Britton, MSN, RN, CNO, Director of the Roanoke Chowan Community Health Center of Ahoskie, NC. Bonnie will present impressive results from the center's telehealth program; this not-for-profit group serves one of the most impoverished and remotely located areas in the nation. Bonnie has stated: "Our goal was to see whether home telehealth systems could cost effectively extend the reach of rural health-care workers."

These remarkable individuals and others with personal experience in this evolving field will be available throughout the meeting for one-on-one discussion.

I hope you will take full advantage of the educational opportunities presented in the newly designed Clinical Resource Center, formerly the exhibit hall. You will find the exhibits, grouped by specialty areas, redesigned to be even more relevant and educational. There will be opportunities to experience the field of telemedicine up close, including ICU telemedicine and the RP-7 robot, which was recently featured in a special TV program on advances in military medicine by Dr. Sanjay Gupta.

I look forward to seeing you in San Diego and hope your educational experience is as rewarding as I anticipate mine to be. The ACCP, with its remarkable volunteer leadership and staff, continues to inspire. ■

Rep Schakowsky Visits Critical Care Family Assistance Program

On August 25, 2009, Representative Janice Schakowsky (D-IL-9) visited Evanston Hospital, part of NorthShore University HealthSystem, in Evanston, IL. As part of her visit, the Congresswoman saw The CHEST Foundation's Critical Care Family Assistance Program (CCFAP) in action, spent time with the ICU staff involved with the CCFAP on a daily basis, and came away with an understanding of the value this program could bring to other ICUs across the United States.

Evanston was one of the first hospitals in the nation to implement this innovative program to fulfill the previously unmet needs of families of critically ill patients in ICUs and foster better communication between the health-care team, patients, and their families.

Representative Schakowsky introduced the *Patient-Focused Critical Care Enhancement Act*, HR 1581, on March 18, 2009, to address the growing critical care workforce shortage. As part of this legislation, the US Department of Health and Human Services would fund similar demonstration projects for the critically ill and their families.

Dr. Jeffery Vender, FCCP, Director of Critical Care Services, and Dr. John Alexander, FCCP, Chief of Cardiac and Thoracic Surgery, both at Evanston Hospital, worked with NorthShore University HealthSystem and the ACCP to organize this event.

Dr. Vender noted, "Having the Congresswoman visit provides great support to our medical team and recognition that NorthShore University HealthSystem and the ACCP are doing the right things for our patients, their families, and our staff." Contact ACCP Health Affairs at healthaffairs@chestnet.org to host a similar event at your institution.

Learn more about the critical care workforce shortage and HR 1581 at www.chestnet.org/practice/advocacy/issues.php.

Learn more about The CHEST Foundation's Critical Care Family Assistance Program at www.chestfoundation.org/foundation/critical/index.php. Learn more about hosting a congressional site visit at http://accpstorage.org/downloads/practice/GR_Toolkit/SiteVisits_3.pdf. ■

Courtesy Jon Hillenbrand, NorthShore University HealthSystem

(L to R) Rep Jan Schakowsky (D-9th/IL); Mark Neaman, President and CEO of NorthShore University HealthSystem; and Dr. John Alexander, FCCP.

NetWorks

Outpatient Oxygen Therapy and Interventional Techniques

Airways Disorders

NetWork Tackles Outpatient Oxygen Therapy

Thirty years ago, there were two options for home oxygen therapy—the big green tank and the little green tank. The big one stayed home, and the little one traveled but not too far and not for too long. The advent of portable liquid oxygen and oxygen concentrators opened up new horizons for patients supported by long-term oxygen therapy.

Today, for patients with COPD, travel is easier, oxygen is more portable, and concentrators no longer have to be plugged into the outlet in the bedroom. While oxygen delivery devices have not changed appreciably since transtracheal and conserving devices became available in the 1990s, home oxygen systems and portable oxygen systems have become smaller, more portable, more practical, and more popular with patients.

Newer devices include the personal liquid oxygen systems. Both the HELiOS Personal Oxygen System (Puritan Bennett Inc; Pleasanton, CA) and the VIAspire Portable (Inspired Technologies Inc; North Huntingdon, PA) consist of small, lightweight components to be used by the patient during daily activities and a high-capacity, no-loss reservoir for refilling, creating a daily supply of liquid oxygen right in the patient's home. These portable units may be connected to the reservoir for continued breathing during sleep, and oxygen deliveries for the reservoir are limited to about eight per year (www.nlhep.org/resources/Prescrb-Hm-Oxygen/home-oxygen-options-4.html. Accessed July 7, 2009). Another viable option is the recently developed oxygen concentrator capable of filling small gas cylinders. The DeVilbiss I-Fill (DeVilbiss Healthcare; Somerset, PA) oxygen tank refill system allows patients to refill any size portable tank in their own homes, virtually ensuring their own supply of oxygen 24/7 (http://respiratory-care-sleep-medicine.advanceweb.com/Editorial/Content/PrintFriendly.aspx?CC=194179. Accessed July 13, 2009).

The HomeFill II Qxygen Delivery System (Invacare; Elyria, OH) is another portable oxygen system that includes a proprietary ML6 cylinder configured with a pneumatic oxygen-conserving device (OCD).

Although concentrators provide a lower F_{IO_2} than USP O_2 tanks, a study showed no statistically significant clinical outcome in patients Sp_{O_2}, heart rate, or Borg scale while using the two different devices (Lewarski et al. *Respir Care* 2003; 48:1115).

A fourth option is the portable oxygen concentrator (POC). Small concentrators, with pulse flow only 1 to 5 liters per minute (LPM) (Inogen One; Inogen; Goleta, CA) or pulse flow of 1 to 6 LPM and/or continuous flow of 0.5 to 3 LPM (Eclipse; SeQual; San Diego, CA) are now FDA-approved and can be operated by using either a standard home electrical outlet or a 12-volt car adapter. A recent study revealed that the mean Sp_{O_2} was equally improved with either the POC or portable liquid oxygen; however, with strenuous exercise, these systems, at 3 LPM, were not sufficient to prevent hypoxemia (Nasilowski et al. *Respir Med* 2008; 102:1021).

The Airways Disorders NetWork is planning a project to develop handouts for physicians and patients addressing the benefits and options of home oxygen therapy. Like the aerosol device handouts, they will be available and updated on the ACCP Web site.

Dr. Jay Peters, FCCP
NetWork Chair
and
Helen M. Sorenson, MA, RRT

Interventional Chest/Diagnostic Procedures

The Interventional Chest/Diagnostic Procedures NetWork evaluates, integrates, and, often, initiates novel, procedure-related diagnostics and therapeutics. A central aim is to provide experience- and evidence-based information for appropriate clinical use as new interventional techniques become disseminated. Several concurrent projects are nearing completion.

The design of an ideal bronchoscopy suite requires an understanding of the specific needs of both interventionists and diagnostic pulmonary physicians. Integration of fluoroscopy, ultrasonography, videobronchoscopy, and speci-

Continued on following page

Special Conflict of Interest Session at CHEST 2009

Wednesday, November 4
10:30 AM-12:00 PM
Conflict of Interest: Where Are We and Where Do We Go?

The past few years have seen increased public concern that real or potential conflicts of interest (COI) may influence content of continuing medical education, research results, and recommendations for clinical practice. In response to such concerns, some members of Congress initiated legislative action to monitor and curb the relationships between physicians and commercial entities, particularly the pharmaceutical industry. In turn, most professional societies, such as the American College of Chest Physicians (ACCP), have increased their efforts to ensure that their products are free of bias. However, since methods to evaluate and manage COI are not yet standardized, professional societies often struggle to define clearly what constitutes COI. This vetting process is further complicated for US-based societies that have a large international membership, because the approach to COI varies from one country to the next.

The ACCP serially evaluates for possible COI those individuals invited to participate in educational programs and guideline panels, as well as those who submit their research findings to *CHEST*. To update its members on these important issues, the ACCP has put together a distinguished panel of experts at CHEST 2009 in San Diego to discuss how COI may affect distribution of medical information and influence health-care policy.

CHEST 2009
October 31 - November 5
San Diego, California

Featured speakers include Dr. Catherine D. DeAngelis, MPH, Editor in Chief, *JAMA*, who will discuss COI and continuing medical education; Dr. Richard Irwin, Master FCCP, Editor in Chief, *CHEST*, who will discuss management of COI at ACCP's journal; Dr. Jim Roach, FCCP, Chief Medical Officer, Momenta Pharmaceuticals, Inc., who will discuss COI from the perspective of industry; and Dr. Ian Nathanson, FCCP, incoming Chair of ACCP Health and Science Policy Committee, who will discuss evaluation and management of COI for ACCP guidelines. ■

Continued from previous page

men preparation areas, as well as ergonomic localization of hardware, needs to be considered. The NetWork is developing a guide that will assist individual institutions and health-care provider systems understand the fiscal and physical plant resource needs for suite design. The NetWork plans to post this document on the ACCP Web site.

It is becoming increasingly apparent that bronchoscopy simulators are important training tools for residents. In a pilot study, residents trained with simulators demonstrated an improved grasp of airway anatomy, and, importantly, appeared to require far less time "practicing on the patient" to become competent bronchoscopists. A manuscript detailing the results is in the final stages of completion.

An initiative to formalize guidelines and metrics for interventional bronchoscopy fellowship training is underway. Currently, no such guidelines exist. An exhaustive review of the NetWork's existing consensus statements is in process. This will include updated reading lists and a reorganization of prior iterations to reflect insight on the use of newer technologies.

Finally, the NetWork encourages ACCP members to visit the Interventional Chest/Diagnostic Procedures NetWork Web pages at www.chestnet.org/networks/icdp/index.php for clinically relevant content, such as "What's Hot?" and "Online Puzzlers."

Dr. Sudish Murthy, FCCP
NetWork Chair

Critical Care Commentary

High-Sensitivity Troponin Measurements and the 99th Percentile Cutoff in the ICU

There is consensus from professionals within the disciplines of cardiology (Thygesen et al. *Circulation* 2007; 116:2634), emergency medicine (Anderson et al. *Circulation* 2007; 116:e148), and laboratory medicine (Morrow et al. *Clin Chem* 2007; 53:552) that cardiac troponin is the gold standard marker for diagnosis and risk stratification for acute coronary syndrome (ACS). These organizations all have endorsed the use of a low troponin cutoff concentration set at the 99th percentile of a healthy population (Figure, cutoff A). Previously, the cutoff concentration was determined using a value that best separated acute myocardial infarction (AMI) from unstable angina (Figure, cutoff B). The cutoff was lowered because it was observed that patients with minor myocardial damage and evidence of myocardial ischemia had the same rate of adverse cardiac events at 30 days and 6 months as those with AMI. Compared with the higher troponin limit, the use of the 99% cutoff enabled detection of more patients at risk for future events (Morrow et al. *JAMA* 2001; 286:2405).

Dr. Neil Halpern, FCCP
Section Editor,
Critical Care Commentary

When the recommendations were first made a decade ago, none of the available troponin assays had the analytical sensitivity to meet these guidelines. Today, most central clinical laboratories have implemented next-generation "high-sensitivity" troponin assays that can meet these recommendations. These assays have shown superior diagnostic utility over conventional troponin assays for diagnosis of AMI, as reported recently (Keller et al. *N Engl J Med* 2009; 361:868; Reichlin et al. *N Engl J Med* 2009; 361:858). Commercial assays detect all troponin forms (free troponin T or I, binary complex of I-C and ternary complex of T-I-C, and fragments) using multiple antibodies directed to the part of the protein that is not degraded in blood (midregion). While the majority of the hospitals have implemented new assays, not all have endorsed the use of the 99th percentile as the ACS cutoff concentration.

From a practical standpoint, the current use of high sensitivity assays and the choice of the 99th percentile as the cutoff for troponin detection raises the following challenges for critical care physicians: (1) How applicable is the 99th percentile cutoff concentration for ICU patients, and (2) what are the consequences of using high-sensitivity assays?

Receiver-operating characteristic (ROC) curve analysis is a statistical treatment that was used to empirically determine the optimum cutoff for troponin (Figure). Lowering the cutoff from the ROC value to 99% has changed the role of troponin from a marker of AMI to an indicator of *any* myocardial damage. For use in the ICU, the objective for troponin testing must be defined in order to determine the appropriate troponin cutoff.

If troponin is used to determine acute myocardial infarction, the 99th percentile may be too low for this population because many ICU patients have minor "non-AMI" cardiac injury due to nonischemic causes, such as renal failure, heart failure, myocarditis, pericarditis, valve disease, sepsis, venous thrombotic disease, GI disease, and use of cardiotoxic drugs (Wu et al. *Clin Chem* 2007; 53:2086). Most investigators believe that the troponin is released from irreversible cardiac damage in these patients with diverse disease etiologies. Any troponin from ischemic injury would be additive to the baseline troponin level that was undetectable with previous generation assays but is now captured with high-sensitivity analysis.

However, if the purpose is to determine the presence of *any* myocardial injury, 99% is appropriate. Irrespective of the etiology of cardiac damage, clinical outcome studies have consistently shown that patients with any increase in troponin have worse clinical outcomes. If therapeutic measures can be taken to minimize poor outcomes in these patients, regular testing with troponin with the 99% cutoff concentrations is warranted. For example, Fernandes (*Crit Care Med* 2009; 37:367) suggested that troponin measurements might be used to identify patients with sepsis who might benefit most from treatment with activated protein C. Serial troponin testing can be helpful in determining if the troponin increases are due to ACS or a chronic, nonischemic etiology. Repeat test results that are within the intraindividual variation of the marker (biologic variation) over the short term would be more indicative of a nonischemic cardiac process (Wu et al. *Clin Chem* 2009; 55:52). A rapid increase in troponin is indicative of acute heart injury, including AMI, but an acute exacerbation of a chronic disease seen in the ICU can also cause a

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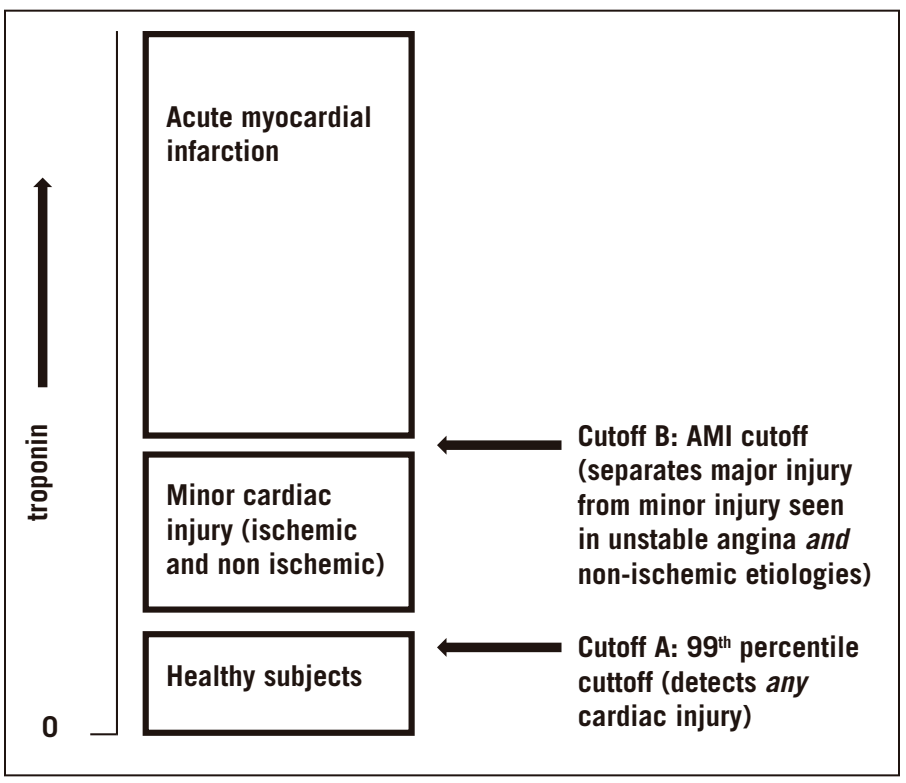

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troponin rise. Critical care physicians must decide if this added sensitivity toward myocardial damage is of value in managing their patients or if it simply adds to diagnostic ambiguity, as large numbers of ICU patients will have minor increases in troponin.

Troponin is useful for diagnosis of ACS because it is assumed that release into the circulation only occurs with irreversible cardiac injury. However, for some ICU patients, there is a suggestion that troponin can be released "without" permanent damage. If true, this might change the perceived value of troponin testing for these patients.

In sepsis, for example, there is release of factors that reduces cardiac function. However, in most cases, myocardial depression is reversible and fully restored among survivors (Rudiger and Singer. *Crit Care Med* 2007; 35:1599). A recent study (Hessel et al. *Pflugers Arch* 2008; 455:979) suggested that troponin I might be released from viable cardiomycytes and mediated by integrins. These adhesion molecules orchestrate cell-to-cell and cell-to-pathogen interactions, and they are known to be increased in patients with sepsis (Hörner et al. *J Surg Res* 2007; 142:59) and, possibly, in other critically ill patients. If troponin can be released without myocardial cell death, or if there are no therapeutic measures that can be taken to reduce morbidity and mortality risks in critically ill patients or those with sepsis, as stratified by troponin, testing in the absence of symptoms suggestive of ACS at any cutoff concentration or testing technology may be unnecessary.

As a middle ground, a consideration could be made for the use of two troponin cutoff concentrations within a hospital. The 99th percentile could be used in the ED for patients who present with acute chest pain and no comorbidities for rule-in or rule-out of AMI. A higher cutoff could be used specifically for the management of ICU patients. For cardiac surgery, some investigators have advocated biomarker cutoff concentrations that are five- to tenfold higher than cutoffs for ambulatory subjects. A separate cutoff might also be useful for predicting a bad clinical outcome in the short term. The assignment of these alternate cutoffs must be empirically determined from sufficiently powered and carefully conducted clinical trials. As an example, Stearns and colleagues (*Anesth Analg* 2009; 108:719) used ROC curves to define a very high troponin cutoff (7.6 ng/mL) to predict adverse events among women undergoing cardiac surgery). While the concept appears sound, the lack of standardization among commercial troponin assays makes this concept difficult to implement globally. Additionally, institutional differences will certainly exist in troponin assays and in the correlation of hospital-based cut-off values with clinical diagnoses or outcomes.

The rate of troponin increase also can be useful in differentiating the release of troponin from chronic cardiac injury or acute myocardial infarction. A recent study (Wu et al. *Clin Chem* 2009; 55:52) on the biological variation of troponin suggests that a >50% increase of troponin or a >30% decline exceeds the variation seen in healthy subjects and suggests that acute injury is occurring.

Currently, there are no guidelines for the use of troponin in ICU patients. While troponin results complement ECG and echocardiographic data, there are no direct correlations. Therefore, the critical care staff must interpret low-level troponin increases with caution, and use results within the context of the sensitivity of the analytic approach and the patient's clinical condition. ■

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Product of The Month

ACCP-SEEK™ Sleep Medicine iPhone® App

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

► POINT COUNTER POINT EDITORIALS: **Point: The Texas Advance Directives Act Effectively and Ethically Resolves Disputes About Medical Futility.** *By Dr. R. Fine* **Counterpoint: The Texas Advance Directives Act Is Ethically Flawed: Medical Futility Disputes Must Be Resolved by a Fair Process.** *By Dr. R. Truog*

EDITORIAL

► **Medical Questionnaires Are Copyrighted To Ensure That Validity Is Maintained.** *By E. F. Juniper*

► **Troponin-Based Risk Stratification of Patients With Acute Nonmassive Pulmonary Embolism: Systematic Review and Meta-analysis.** *By Dr. D. Jiménez, et al.*

► **In-Hospital Treatment of Obstructive Sleep Apnea During Decompensation of Heart Failure.** *By Dr. R. N. Khayat, et al.*

► **Exhaled Air Dispersion Distances During Noninvasive Ventilation via Different Respironics Face Masks.** *By Dr. D. S. Hui, et al.*

► **Increases in Endotracheal Tube Resistance Are Unpredictable Relative to Duration of Intubation.** *By Dr. A. M. Wilson, et al.*

► **Effect of the Management of Patients With Chronic Cough by Pulmonologists and Certified Respiratory Educators on Quality of Life: A Randomized Trial.** *By Dr. S. K. Field, FCCP, et al.*

► **Safety and Efficacy of Combined Long-acting Beta-Agonists and Inhaled Corticosteroids vs Long-acting Beta-Agonists Monotherapy for Stable COPD: A Systematic Review.** *By Dr. G. J. Rodrigo, et al.*

www.chestjournal.org

FCCP Receives Honorary Doctorate From Mongolia

Dr. John R. Handy, Jr., FCCP, Director, Providence Thoracic Surgery Program; and Co-Director, Providence Thoracic Oncology Program, Thoracic and Cardiovascular Surgery, The Oregon Clinic, Portland, was recently awarded an honorary doctorate for his mission work by the National Medical Research Institute of Mongolia.

Only seven other honorary doctorates have been awarded in the 50 years of the Institute's existence.

Dr. Handy was joined by cardiac anesthesiologist Dr. Patricia Gramling-Babb on a medical mission trip to Mongolia in May.

Dr. Handy and Dr. Gramling-Babb, who is Assistant Professor of Clinical Anesthesia at the University of Illinois College of Medicine in Chicago, led a team that went to Mongolia to perform cardiac and thoracic surgery.

Dr. Gramling-Babb also received the honorary degree.

The two physicians are members of earthMed (www.earthmed.org), a philanthropic health-care organization whose goal is to improve medical care in developing countries by program development, education, and direct patient care through medical volunteers.

"We have been performing surgery in Mongolia for the better part of 10 years. It is extremely rewarding professionally and personally," Dr. Handy said.

"No one was more surprised than us when we were awarded the doctorates," Dr. Handy commented.

The honorary degrees were awarded to Dr. Handy and Dr. Gramling-Babb by Nachin Baasanjav, PhD, DSc(Med), Director of the National Institute of Health Mongolia, on the basis of 8 years of "selfless contributions to the development of cardiothoracic surgery in Mongolia." ■

Donate Your Honoraria to The CHEST Foundation

ACCP members and CHEST faculty have been generously donating their honoraria to The CHEST Foundation for many years.

This method of contributing has proven to be an easy way for donors to give to The Foundation while they enjoy the professional interaction with their peers at ACCP educational programs and pharmaceutical focus groups.

Those contributing their honorarium to The CHEST Foundation are supporting The Foundation's four areas of focus: tobacco prevention, clinical research, humanitarian service, and critical care/end-of-life care.

This fall, ACCP members can direct their honorarium to a new campaign developed by Jay I. Peters, MD, FCCP – Physicians Speaking for Humanity or PS4H.

PS4H is an appeal to physicians who lecture and/or attend pharmaceutical focus groups to donate their honorariums to The CHEST Foundation to support the pro bono service of fellow ACCP members through The Foundation's Humanitarian Service Program.

Prior to CHEST 2009, CHEST faculty members can indicate online that all or a portion of their honorarium should be made payable to The CHEST Foundation.

The designated amount will automatically be given to The Foundation as a charitable contribution in their name, and any remainder due will processed and mailed by the ACCP.

This donation clearly benefits The Foundation and may be a benefit to you by reducing your annual income at year-end.

Canadian members donating in this way are allowed to donate US income and claim the eligible amount of the gift allowed on a US tax return, up to 75% of the net US income on a Canadian tax return.

If you are interested in donating honoraria received as faculty at CHEST 2009 or at outside Pharma engagements to The CHEST Foundation's annual fund or the PS4H campaign, contact Teri Ruiz at truiz@chestnet.org or (847) 498-8308. ■

ZYVOX® linezolid injection, tablets and for oral suspension Brief summary of prescribing information.

INDICATIONS AND USAGE ZYVOX formulations are indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms (**see PRECAUTIONS, Pediatric Use**). **Vancomycin-Resistant *Enterococcus faecium* infections**, including cases with concurrent bacteremia. **Nosocomial pneumonia** caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), or *Streptococcus pneumoniae* (including multidrug-resistant strains [MDRSP*]). **Complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis**, caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*. ZYVOX has not been studied in the treatment of decubitus ulcers. **Uncomplicated skin and skin structure infections** caused by *Staphylococcus aureus* (methicillin-susceptible only) or *Streptococcus pyogenes*. **Community-acquired pneumonia** caused by *Streptococcus pneumoniae* (including multidrug-resistant strains [MDRSP*]), including cases with concurrent bacteremia, or *Staphylococcus aureus* (methicillin-susceptible strains only). To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZYVOX and other antibacterial drugs, ZYVOX should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy. **CONTRAINDICATIONS** ZYVOX formulations are contraindicated for use in patients who have known hypersensitivity to linezolid or any of the other product components. ZYVOX should not be used in patients taking any medicinal product which inhibits monoamine oxidases A or B (e.g. phenelzine, isocarboxazid) or within 2 weeks of taking any such medicinal product. Unless patients are monitored for potential increases in blood pressure, ZYVOX should not be administered to patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis and/or patients taking any of the following types of medications: directly and indirectly acting sympathomimetic agents (e.g. pseudoephedrine), vasopressive agents (e.g. epinephrine, norepinephrine), and dopaminergic agents (e.g. dopamine, dobutamine). Unless patients are carefully observed for signs and/or symptoms of serotonin syndrome, ZYVOX should not be administered to patients with carcinoid syndrome and/or patients taking any of the following medications: serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), meperidine, or buspirone. **WARNINGS Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported in patients receiving ZYVOX. In cases where the outcome is known, when ZYVOX was discontinued, the affected hematologic parameters have risen toward pretreatment levels. Complete blood counts should be monitored weekly in patients who receive ZYVOX, particularly in those who receive ZYVOX for longer than two weeks, those with pre-existing myelosuppression, those receiving concomitant drugs that produce bone marrow suppression, or those with a chronic infection who have received previous or concomitant antibiotic therapy. Discontinuation of therapy with ZYVOX should be considered in patients who develop or have worsening myelosuppression.** In adult and juvenile dogs and rats, myelosuppression, reduced extramedullary hematopoiesis in spleen and liver, and lymphoid depletion of thymus, lymph nodes, and spleen were observed. **Mortality Imbalance in an Investigational Study in Patients With Catheter-related Bloodstream Infections, Including Those With Catheter-site Infections**. ZYVOX is not approved and should not be used for the treatment of patients with catheter-related bloodstream infections or catheter-site infections. In an open-label investigational study in seriously ill patients with intravascular catheter-related infections, an imbalance in mortality was seen in patients treated with ZYVOX compared with vancomycin/dicloxacillin/oxacillin. While causality has not been established, mortality was higher in patients treated with ZYVOX who were infected with Gram-negative organisms alone, with both Gram-positive and Gram-negative organisms, or who had no infection when they entered the study. Patients with Gram-positive infections had no difference in mortality. ZYVOX has no clinical activity against Gram-negative pathogens and is not indicated for the treatment of Gram-negative infections. It is critical that specific Gram-negative therapy be initiated immediately if a concomitant Gram-negative pathogen is documented or suspected. *Clostridium difficile*–associated diarrhea (CDAD) has been reported with the use of nearly all antibacterial agents, including ZYVOX, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C difficile*. *C difficile* produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing strains of *C difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur more than 2 months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C difficile*, and surgical evaluation should be instituted as clinically indicated. **PRECAUTIONS General Lactic acidosis has been reported with the use of ZYVOX. In reported cases, patients experienced repeated episodes of nausea and vomiting. Patients who develop recurrent nausea or vomiting, unexplained acidosis, or a low bicarbonate level while receiving ZYVOX should receive immediate medical evaluation. Spontaneous reports of serotonin syndrome associated with the co-administration of ZYVOX and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported (see PRECAUTIONS, Drug Interactions). Where administration of ZYVOX and concomitant serotonergic agents is clinically appropriate, patients should be closely observed for signs and symptoms of serotonin syndrome such as cognitive dysfunction, hyperpyrexia, hyperreflexia and incoordination. If signs or symptoms occur physicians should consider discontinuation of either one or both agents. If the concomitant serotonergic agent is withdrawn, discontinuation symptoms can be observed (see package insert of the specified agent(s) for a description of the associated discontinuation symptoms).** Peripheral and optic neuropathy have been reported in patients treated with ZYVOX, primarily those patients treated for longer than the maximum recommended duration of 28 days. In cases of optic neuropathy that progressed to loss of vision, patients were treated for extended periods beyond the maximum recommended duration. Visual blurring has been reported in some patients treated with ZYVOX for less than 28 days. If patients experience symptoms of visual impairment, such as changes in visual acuity, changes in color vision, blurred vision, or visual field defect, prompt ophthalmic evaluation is recommended. **Visual function should be monitored in all patients taking ZYVOX for extended periods (≥3 months) and in all patients reporting new visual symptoms regardless of length of therapy with ZYVOX.** If peripheral or optic neuropathy occurs, the continued use of ZYVOX in these patients should be weighed against the potential risks. Convulsions have been reported in patients treated with ZYVOX. In some of these cases, a history of seizures or risk factors for seizures was reported. The use of antibiotics may promote the overgrowth of nonsusceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken. ZYVOX has not been studied in patients with uncontrolled hypertension, pheochromocytoma, carcinoid syndrome, or untreated hyperthyroidism. The safety and efficacy of ZYVOX formulations given for longer than 28 days have not been evaluated in controlled clinical trials. Prescribing ZYVOX in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. **Information for Patients** Patients should be advised that: ZYVOX may be taken with or without food. They should inform their physician if they have a history of hypertension. Large quantities of foods or beverages with high tyramine content should be avoided while taking ZYVOX. Quantities of tyramine consumed should be less than 100 mg per meal. Foods high in tyramine content include those that may have undergone protein changes by aging, fermentation, pickling, or smoking to improve flavor, such as aged cheeses (0 to 15 mg tyramine per ounce); fermented or air-dried meats (0.1 to 8 mg tyramine per ounce); sauerkraut (8 mg tyramine per 8 ounces); soy sauce (5 mg tyramine per 1 teaspoon); tap beers (4 mg tyramine per 12 ounces); red wines (0 to 6 mg tyramine per 8 ounces). The tyramine content of any protein-rich food may be increased if stored for long periods or improperly refrigerated. They should inform their physician if taking medications containing pseudoephedrine HCl or phenylpropanolamine HCl, such as cold remedies and decongestants. They should inform their physician if taking serotonin re-uptake inhibitors or other antidepressants. *Phenylketonurics:* Each 5 mL of the 100 mg/5 mL ZYVOX for Oral Suspension contains 20 mg phenylalanine. The other ZYVOX formulations do not contain phenylalanine. Contact your physician or pharmacist. They should inform their physician if they experience changes in vision. They should inform their physician if they have a history of seizures. Diarrhea is a common problem caused by antibiotics, which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible. Patients should be counseled that antibacterial drugs including ZYVOX should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When ZYVOX is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by ZYVOX or other antibacterial drugs in the future. **Drug Interactions *Monoamine Oxidase Inhibition:*** Linezolid is a reversible, nonselective inhibitor of monoamine oxidase. Therefore, linezolid has the potential for interaction with adrenergic and serotonergic agents. *Adrenergic Agents:* Some individuals receiving ZYVOX may experience a reversible enhancement of the pressor response to indirect-acting sympathomimetic agents, vasopressor or dopaminergic agents. Commonly used drugs such as phenylpropanolamine and pseudoephedrine have been specifically studied. Initial doses of adrenergic agents, such as dopamine or epinephrine, should be reduced and titrated to achieve the desired response. *Serotonergic Agents:* Co-administration of linezolid and serotonergic agents was not associated with serotonin syndrome in Phase 1, 2 or 3 studies. Spontaneous reports of serotonin syndrome associated with co-administration of ZYVOX and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported. Patients who are treated with ZYVOX and concomitant serotonergic agents should be closely observed as described in the PRECAUTIONS, General Section. **Drug-Laboratory Test Interactions** There are no reported drug-laboratory test interactions. **Pregnancy Teratogenic Effects. Pregnancy Category C:** Linezolid was not teratogenic in mice, rats, or rabbits at exposure levels 6.5-fold (in mice), equivalent to (in rats), or 0.5-fold (in rabbits) the expected human exposure level, based on AUCs. However, embryo and fetal toxicities were seen (see **Non-teratogenic Effects**). There are no adequate and well-controlled studies in pregnant women. ZYVOX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Non-teratogenic Effects** In mice, embryo and fetal toxicities were seen only at doses that caused maternal toxicity (clinical signs and reduced body weight gain). A dose of 450 mg/kg/day (6.5-fold the estimated human exposure level based on AUCs) correlated with increased postimplantational embryo death, including total litter loss, decreased fetal body weights, and an increased incidence of costal cartilage fusion. In rats, mild fetal toxicity was observed at 15 and 50 mg/kg/day (exposure levels 0.22-fold to approximately equivalent to the estimated human exposure, respectively based on AUCs). The effects consisted of decreased fetal body weights and reduced ossification of sternebrae, a finding often seen in association with decreased fetal body weights. Slight maternal toxicity, in the form of reduced body weight gain, was seen at 50 mg/kg/day. In rabbits, reduced fetal body weight occured only in the presence of maternal toxicity (clinical signs, reduced body weight gain and food consumption) when administered at a dose of 15 mg/kg/day (0.5-fold the estimated human exposure based on AUCs). When female rats were treated with 50 mg/kg/day (approximately equivalent to the estimated human exposure based on AUCs) of linezolid during pregnancy and lactation, survival of pups was decreased on postnatal days 1 to 4. Male and female pups permitted to mature to reproductive age, when mated, showed an increase in preimplantation loss. **Nursing Mothers** Linezolid and its metabolites are excreted in the milk of lactating rats. Concentrations in milk were similar to those in maternal plasma. It is not known whether linezolid is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZYVOX is administered to a nursing woman. **Pediatric Use** The safety and effectiveness of ZYVOX for the treatment of pediatric patients with the following infections are supported by evidence from adequate and well-controlled studies in adults, pharmacokinetic data in pediatric patients, and additional data from a comparator-controlled study of Gram-positive infections in pediatric patients ranging in age from birth through 11 years (see **INDICATIONS AND USAGE**): nosocomial pneumonia, complicated skin and skin structure infections, community-acquired pneumonia (also supported by evidence from an uncontrolled study in patients ranging in age from 8 months through 12 years), vancomycin-resistant *Enterococcus faecium* infections. The safety and effectiveness of ZYVOX for the treatment of pediatric patients with the following infection have been established in a comparator-controlled study in pediatric patients ranging in age from 5 through 17 years: uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible strains only) or *Streptococcus pyogenes*. Pharmacokinetic information generated in pediatric patients with ventriculoperitoneal shunts showed variable cerebrospinal fluid (CSF) linezolid concentrations following single and multiple dosing of linezolid; therapeutic concentrations were not consistently achieved or maintained in the CSF. Therefore, the use of linezolid for the empiric treatment of pediatric patients with central nervous system infections is not recommended. The C_{max} and the volume of distribution (Vss) of linezolid are similar regardless of age in pediatric patients. However, linezolid clearance is a function of age. Excluding neonates less than a week of age, clearance is most rapid in the youngest age groups ranging from >1 week old to 11 years, resulting in lower single-dose systemic exposure (AUC) and shorter half-life as compared with adults. As age of pediatric patients increases, the clearance of linezolid gradually decreases, and by adolescence, mean clearance values approach those observed for the adult population. There is wider inter-subject variability in linezolid clearance and in systemic drug exposure (AUC) across all pediatric age groups as compared with adults. Similar mean daily AUC values were observed in pediatric patients from birth to 11 years of age dosed q8h relative to adolescents or adults dosed q12h. Therefore, the dosage for pediatric patients up to 11 years of age should be 10 mg/kg q8h. Pediatric patients 12 years and older should receive 600 mg q12h. Recommendations for the dosage regimen for pre-term neonates less than 7 days of age (gestational age less than 34 weeks) are based on pharmacokinetic data from 9 pre-term neonates. Most of these pre-term neonates have lower systemic linezolid clearance values and larger AUC values than many full-term neonates and older infants. Therefore, these pre-term neonates should be initiated with a dosing regimen of 10 mg/kg q12h. Consideration may be given to the use of a 10 mg/kg q8h regimen in neonates with a sub-optimal clinical response. All neonatal patients should receive 10 mg/kg q8h by 7 days of life. In limited clinical experience, 5 out of 6 (83%) pediatric patients with infections due to Gram-positive pathogens with MICs of 4 µg/mL treated with ZYVOX had clinical cures. However, pediatric patients exhibit wider variability in linezolid clearance and systemic exposure (AUC) compared with adults. In pediatric patients with a sub-optimal clinical response, particularly those with pathogens with MIC of 4 µg/mL, lower systemic exposure, site and severity of infection, and the underlying medical condition should be considered when assessing clinical response. **Geriatric Use** Of the 2046 patients treated with ZYVOX in Phase 3 comparator-controlled clinical trials, 589 (29%) were 65 years or older and 253 (12%) were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients. **ADVERSE REACTIONS Adult Patients** The safety of ZYVOX formulations was evaluated in 2046 adult patients enrolled in seven Phase 3 comparator-controlled clinical trials, who were treated for up to 28 days. In these studies, 85% of the adverse events reported with ZYVOX were described as mild to moderate in intensity. The incidence (%) of adverse events reported in at least 2% of patients treated with either ZYVOX (n=2046) or all comparators† (n=2001) in these trials were as follows: diarrhea 8.3 and 6.3; headache 6.5 and 5.5; nausea 6.2 and 4.6; vomiting 3.7 and 2.0; insomnia 2.5 and 1.7; constipation 2.2 and 2.1; rash 2.0 and 2.2; dizziness 2.0 and 1.9; and fever 1.6 and 2.1 respectively. The most common adverse events in patients treated with ZYVOX were diarrhea (incidence across studies: 2.8% to 11.0%), headache (incidence across studies: 0.5% to 11.3%), and nausea (incidence across studies: 3.4% to 9.6%). The percent of drug-related adverse events in at least 1% of adult patients in a trial involving the treatment of uncomplicated skin and skin structure infection comparing ZYVOX 400 mg q12h (n=548) to clarithromycin 250 mg q12h (n=537) were 25.4 and 19.6 respectively. The percent of patients discontinuing drug due to drug-related adverse events‡ were 3.5 and 2.4 respectively. The incidence of drug-related adverse events occurring in >1% of adult patients were diarrhea 5.3 and 4.8; nausea 3.5 and 3.5; headache 2.7 and 2.2; taste alteration 1.8 and 2.0; vaginal moniliasis 1.6 and 1.3; fungal infection 1.5 and 0.2; abnormal liver function tests 0.4 and 0.0; vomiting 0.9 and 0.4; tongue discoloration 1.1 and 0.0; dizziness 1.1 and 1.5; and oral moniliasis 0.4 and 0.0 respectively. The percent of drug-related adverse events in at least 1% of adult patients in all other indications of ZYVOX 600 mg q12h (n=1498) versus all other comparators§ (n=1464) with at least 1 drug-related adverse event was 20.4 and 14.3 respectively. The percent of adult patients discontinuing due to drug-related adverse events‡ was 2.1 and 1.7 respectively. The incidence of drug-related adverse events occurring in >1% of adult patients were diarrhea 4.0 and 2.7; nausea 3.3 and 1.8; headache 1.9 and 1.0; taste alteration 0.9 and 0.2; vaginal moniliasis 1.0 and 0.4; fungal infection 0.1 and <0.1; abnormal liver function tests 1.3 and 0.5; vomiting 1.2 and 0.4; tongue discoloration 0.2 and 0.0; dizziness 0.4 and 0.3; and oral moniliasis 1.1 and 0.4. Other adverse events reported in Phase 2 and Phase 3 studies included oral moniliasis, vaginal moniliasis, hypertension, dyspepsia, localized abdominal pain, pruritus, and tongue discoloration. **Pediatric Patients** The safety of ZYVOX formulations was evaluated in 215 pediatric patients ranging in age from birth through 11 years, and in 248 pediatric patients aged 5 through 17 years (146 of these 248 were age 5 through 11 and 102 were age 12 to 17). These patients were enrolled in two Phase 3 comparator-controlled clinical trials and were treated for up to 28 days. In these studies, 83% and 99%, respectively, of the adverse events reported with ZYVOX were described as mild to moderate in intensity. In the study of hospitalized pediatric patients (birth through 11 years) with Gram-positive infections, who were randomized 2 to 1 (linezolid:vancomycin), mortality was 6.0% (13/215) in the linezolid arm and 3.0% (3/101) in the vancomycin arm. However, given the severe underlying illness in the patient population, no causality could be established. The incidence of adverse events reported in ≥2% of pediatric patients treated for uncomplicated skin and skin structure infections‖ with ZYVOX (n=248) or cefadroxil (n= 251) were fever 2.9 and 3.6; diarrhea 7.8 and 8.0; vomiting 2.9 and 6.4; rash 1.6 and 1.2; headache 6.5 and 4.0; upper respiratory infection 3.7 and 5.2; nausea 3.7 and 3.2; trauma 3.3 and 4.8; pharyngitis 2.9 and 1.6; cough 2.4 and 4.0; generalized abdominal pain 2.4 and 2.8; localized abdominal pain 2.4 and 2.8; loose stools 1.6 and 0.8; localized pain 2.0 and 1.6; skin disorder 2.0 and 0.0 respectively. The incidence of adverse events reported in ≥2% of pediatric patients treated for all other indications¶ with either ZYVOX (n=215) or vancomycin (n=101) in comparator-controlled trials were fever 14.1 and 14.1; diarrhea 10.8 and 12.1; vomiting 9.4 and 9.1; sepsis 8.0 and 7.1; rash 7.0 and 15.2; headache 0.9 and 0.0; anemia 5.6 and 7.1; thrombocytopenia 4.7 and 2.0; upper respiratory infection 4.2 and 1.0; nausea 1.9 and 0.0; dyspnea 3.3 and 1.0; reaction at site of injection or of vascular catheter 3.3 and 5.1; trauma 2.8 and 2.0; pharyngitis 0.5 and 1.0; convulsion 2.8 and 2.0; hypokalemia 2.8 and 3.0; pneumonia 2.8 and 2.0; thrombocythemia 2.8 and 2.0; cough 0.9 and 0.0; generalized abdominal pain 0.9 and 2.0; localized abdominal pain 0.5 and 1.0; apnea 2.3 and 2.0; gastrointestinal bleeding 2.3 and 1.0; generalized edema 2.3 and 1.0; loose stools 2.3 and 3.0; localized pain 0.9 and 0.0; and skin disorder 0.9 and 1.0. The percent of pediatric patients treated for uncomplicated skin and skin structure infections‖ with either ZYVOX (n=248) or cefadroxil (n=251) and with ≥1 drug-related adverse event occurring in more than 1% of patients were 19.2 and 14.1 respectively. The percent of pediatric patients discontinuing due to a drug-related adverse event was 1.6 and 2.4 respectively. The incidence of drug-related adverse events reported in more than 1% of pediatric patients (and more than 1 patient) were diarrhea 5.7 and 5.2; nausea 3.3 and 2.0; headache 2.4 and 0.8; loose stools 1.2 and 0.8; vomiting 1.2 and 2.4; generalized abdominal pain 1.6 and 1.2; localized abdominal pain 1.6 and 1.2; eosinophilia 0.4 and 0.4; rash 0.4 and 1.2; vertigo 1.2 and 0.4 and pruritus at non-application site 0.4 and 0.0 respectively. The percent of pediatric patients treated for all other indications¶ with either ZYVOX (n=215) or vancomycin (n=101) and with ≥1 drug-related adverse event occurring in more than 1% of patients were 18.8 and 34.3 respectively. The percent of patients discontinuing due to a drug-related adverse event were 0.9 and 6.1 respectively. The incidence of drug-related adverse events reported in more than 1% of pediatric patients (and more than 1 patient) were diarrhea 3.8 and 6.1; nausea 1.4 and 0.0; loose stools 1.9 and 0.0; thrombocytopenia 1.9 and 0.0; vomiting 1.9 and 1.0; anemia 1.4 and 1.0; eosinophilia 1.4 and 0.0; rash 1.4 and 7.1; oral moniliasis 0.9 and 4.0; fever 0.5 and 3.0; pruritus at non-application site 0.0 and 2.0; and anaphylaxis 0.0 and 10.1# respectively. **Laboratory Changes** ZYVOX has been associated with thrombocytopenia when used in doses up to and including 600 mg every 12 hours for up to 28 days. In Phase 3 comparator-controlled trials, the percentage of adult patients who developed a substantially low platelet count (defined as less than 75% of lower limit of normal and/or baseline) was 2.4% (range among studies: 0.3 to 10.0%) with ZYVOX and 1.5% (range among studies: 0.4 to 7.0%) with a comparator. In a study of hospitalized pediatric patients ranging in age from birth through 11 years, the percentage of patients who developed a substantially low platelet count (defined as less than 75% of lower limit of normal and/or baseline) was 12.9% with ZYVOX and 13.4% with vancomycin. In an outpatient study of pediatric patients aged from 5 through 17 years, the percentage of patients who developed a substantially low platelet count was 0% with ZYVOX and 0.4% with cefadroxil. Thrombocytopenia associated with the use of ZYVOX appears to be dependent on duration of therapy, (generally greater than 2 weeks of treatment). The platelet counts for most patients returned to the normal range/baseline during the follow-up period. No related clinical adverse events were identified in Phase 3 clinical trials in patients developing thrombocytopenia. Bleeding events were identified in thrombocytopenic patients in a compassionate use program for ZYVOX; the role of linezolid in these events cannot be determined (see **WARNINGS**). Changes seen in other laboratory parameters, without regard to drug relationship, revealed no substantial differences between ZYVOX and the comparators. These changes were generally not clinically significant, did not lead to discontinuation of therapy, and were reversible. The percent of adult patients with at least one substantially abnormal hematologic** value in patients treated with ZYVOX 400 mg q12h or clarithromycin 250 mg q12h for uncomplicated skin and skin structure infections were as follows: hemoglobin (g/dL) 0.9 and 0.0; platelet count (x 10^3/mm^3) 0.7 and 0.8; WBC (x 10^3/mm^3) 0.2 and 0.6; neutrophils (x 10^3/mm^3) 0.0 and 0.2 respectively. The percent of adult patients with at least one substantially abnormal hematologic** value in patients treated with ZYVOX 600 mg q12h or a comparator§ were as follows: hemoglobin (g/dL) 7.1 and 6.6; platelet count (x 10^3/mm^3) 3.0 and 1.8; WBC (x 10^3/mm^3) 2.2 and 1.3 and neutrophils (x 10^3/mm^3) 1.1 and 1.2 respectively. The percent of adult patients with at least one substantially abnormal serum chemistry†† value in patients treated with ZYVOX 400 mg q12h or clarithromycin 250 mg q12h for uncomplicated skin and skin structure infections were as follows: AST (U/L) 1.7 and 1.3; ALT (U/L) 1.7 and 1.7; LDH (U/L) 0.2 and 0.2; alkaline phosphatase (U/L) 0.2 and 0.2; lipase (U/L) 2.8 and 2.6; amylase (U/L) 0.2 and 0.2; total bilirubin (mg/dL) 0.2 and 0.0; BUN (mg/dL) 0.2 and 0.0; and creatinine (mg/dL) 0.2 and 0.0 respectively. The percent of adult patients with at least one substantially abnormal serum chemistry†† value in patients treated with ZYVOX 600 mg q12h or a comparator§ were as follows: AST (U/L) 5.0 and 6.8; ALT (U/L) 9.6 and 9.3; LDH (U/L) 1.8 and 1.5; alkaline phosphatase (U/L) 3.5 and 3.1; lipase (U/L) 4.3 and 4.2; amylase (U/L) 2.4 and 2.0; total bilirubin (mg/dL) 0.9 and 1.1; BUN (mg/dL) 2.1 and 1.5; and creatinine (mg/dL) 0.2 and 0.6 respectively. The percent of pediatric patients with at least one substantially abnormal hematologic‡‡ value in patients treated with ZYVOX or cefadroxil for uncomplicated skin and skin structure infections‖ were as follows: hemoglobin (g/dL) 0.0 and 0.0; platelet count (x 10^3/mm^3) 0.0 and 0.4; WBC (x 10^3/mm^3) 0.8 and 0.8; neutrophils (x 10^3/mm^3) 1.2 and 0.8 respectively. The percent of pediatric patients with at least one substantially abnormal hematologic‡‡ value in patients treated with ZYVOX or vancomycin for any other indication¶ were as follows: hemoglobin (g/dL) 15.7 and 12.4; platelet count (x 10^3/mm^3) 12.9 and 13.4; WBC (x 10^3/mm^3) 12.4 and 10.3 and neutrophils (x 10^3/mm^3) 5.9 and 4.3 respectively. The percent of pediatric patients with at least one substantially abnormal serum chemistry^a^ value in patients treated with ZYVOX or cefadroxil for uncomplicated skin and skin structure infections‖ were as follows: ALT (U/L) 0.0 and 0.0; lipase (U/L) 0.4 and 1.2; and creatinine (mg/dL) 0.4 and 0.0 respectively. The percent of pediatric patients with at least one substantially abnormal serum chemistry^a^ value in patients treated with ZYVOX or vancomycin for any other indication¶ were as follows: ALT (U/L) 10.1 and 12.5; amylase (U/L) 0.6 and 1.3; total bilirubin (mg/dL) 6.3 and 5.2; and creatinine (mg/dL) 2.4 and 1.0 respectively. **Postmarketing Experience** Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported during postmarketing use of ZYVOX (see **WARNINGS**). Peripheral neuropathy, and optic neuropathy sometimes progressing to loss of vision, have been reported in patients treated with ZYVOX. Lactic acidosis has been reported with the use of ZYVOX (see **PRECAUTIONS**). Although these reports have primarily been in patients treated for longer than the maximum recommended duration of 28 days, these events have also been reported in patients receiving shorter courses of therapy. Serotonin syndrome has been reported in patients receiving concomitant serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and ZYVOX (see **PRECAUTIONS**). Convulsions have been reported with the use of ZYVOX (see **PRECAUTIONS**). Anaphylaxis, angioedema, and bullous skin disorders such as those described as Stevens Johnson syndrome have been reported. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to ZYVOX, or a combination of these factors. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made and causal relationship cannot be precisely established. **OVERDOSAGE** In the event of overdosage, supportive care is advised, with maintenance of glomerular filtration. Hemodialysis may facilitate more rapid elimination of linezolid. In a Phase 1 clinical trial, approximately 30% of a dose of linezolid was removed during a 3-hour hemodialysis session beginning 3 hours after the dose of linezolid was administered. Data are not available for removal of linezolid with peritoneal dialysis or hemoperfusion. Clinical signs of acute toxicity in animals were decreased activity and ataxia in rats and vomiting and tremors in dogs treated with 3000 mg/kg/day and 2000 mg/kg/day, respectively.

* MDRSP refers to isolates resistant to 2 or more of the following antibiotics: penicillin, second-generation cephalosporins, macrolides, tetracycline, and trimethoprim/sulfamethoxazole.

† Comparators included cefpodoxime proxetil 200 mg PO q12h; ceftriaxone 1 g IV q12h; clarithromycin 250 mg PO q12h; dicloxacillin 500 mg PO q6h; oxacillin 2 g IV q6h; vancomycin 1 g IV q12h.

‡ The most commonly reported drug-related adverse events leading to discontinuation in patients treated with ZYVOX were nausea, headache, diarrhea, and vomiting.

§ Comparators included cefpodoxime proxetil 200 mg PO q12h; ceftriaxone 1 g IV q12h; dicloxacillin 500 mg PO q6h; oxacillin 2 g IV q6h; vancomycin 1 g IV q12h.

‖ Patients 5 through 11 years of age received ZYVOX 10 mg/kg PO q12h or cefadroxil 15 mg/kg PO q12h. Patients 12 years or older received ZYVOX 600 mg PO q12h or cefadroxil 500 mg PO q12h.

¶ Patients from birth through 11 years of age received ZYVOX 10 mg/kg IV/PO q8h or vancomycin 10 to 15 mg/kg IV q6-24h, depending on age and renal clearance.

These reports were of 'red-man syndrome,' which were coded as anaphylaxis.

** <75% (<50% for neutrophils) of Lower Limit of Normal (LLN) for values normal at baseline; <75% (<50% for neutrophils) of LLN and of baseline for values abnormal at baseline.

†† >2 x Upper Limit of Normal (ULN) for values normal at baseline; >2 x ULN and >2 x baseline for values abnormal at baseline.

‡‡ <75% (<50% for neutrophils) of Lower Limit of Normal (LLN) for values normal at baseline; <75% (<50% for neutrophils) of LLN and <75% (<50% for neutrophils, <90% for hemoglobin if baseline <LLN) of baseline for values abnormal at baseline.

^a^ >2 x Upper Limit of Normal (ULN) for values normal at baseline; >2 x ULN and >2 (>1.5 for total bilirubin) x baseline for values abnormal at baseline.

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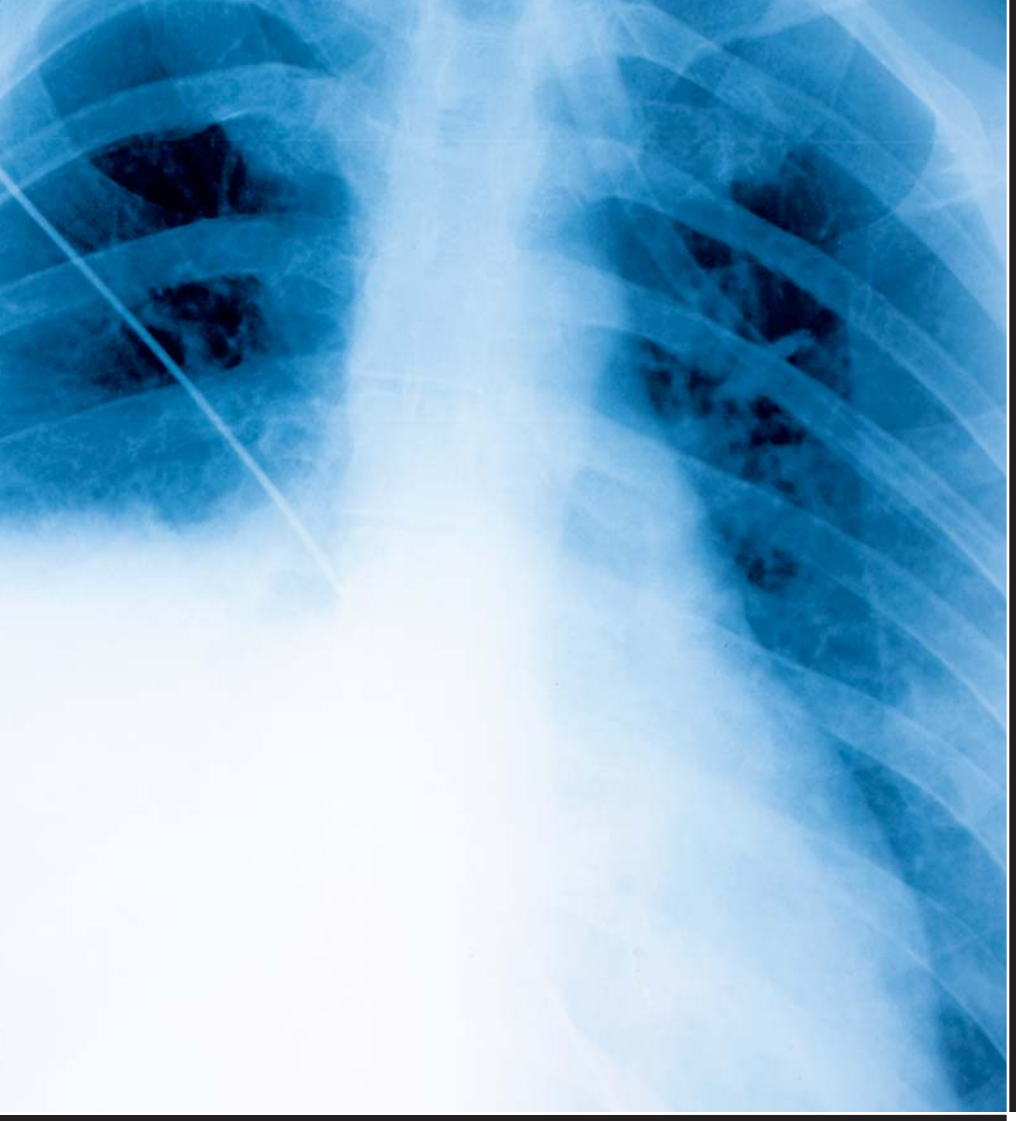
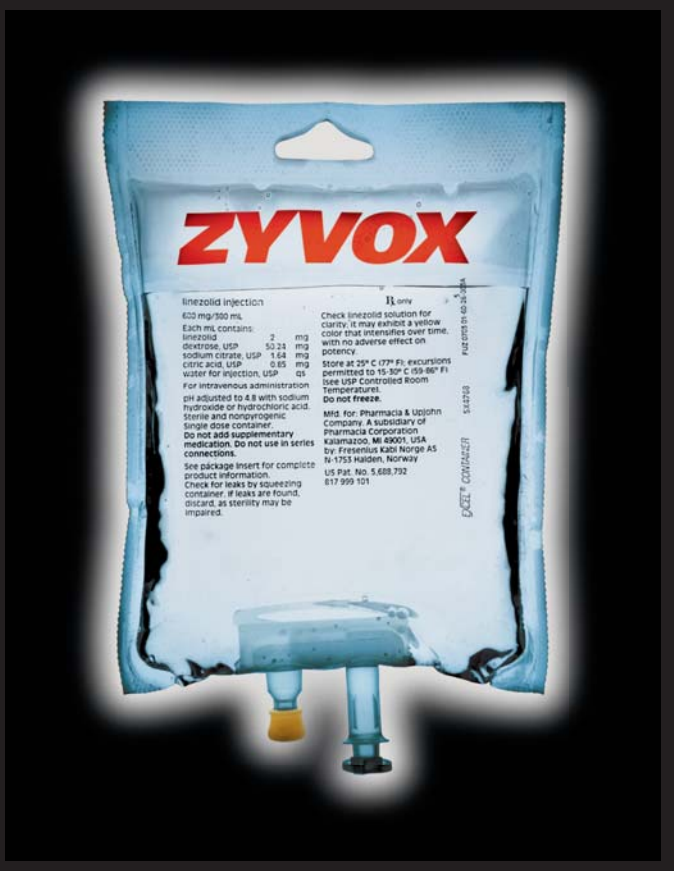


SERIOUS INFECTION



SERIOUS RESULTS

ZYVOX—proven efficacy in nosocomial pneumonia, due to known or suspected MRSA[1-3]*

ZYVOX is indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms:

Nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains) or *Streptococcus pneumoniae* (including multidrug-resistant strains [MDRSP]).

Complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis, caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*. ZYVOX has not been studied in the treatment of decubitus ulcers.

ZYVOX should not be used in patients taking any medicinal product which inhibits monoamine oxidases A or B (e.g. phenelzine, isocarboxazid) or within 2 weeks of taking any such product.

Unless patients are monitored for potential increases in blood pressure, ZYVOX should not be administered to patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis and/or patients taking any of the following: directly and indirectly acting sympathomimetic, vasopressive, and dopaminergic agents.

Unless patients are carefully observed for signs and/or symptoms of serotonin syndrome, ZYVOX should not be administered to patients with carcinoid syndrome and/or patients taking any of the following medications: serotonin reuptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists, meperidine, or buspirone.

Spontaneous reports of serotonin syndrome have been reported with the coadministration of ZYVOX and serotonergic agents. If signs or symptoms of serotonin syndrome, such as cognitive dysfunction, hyperpyrexia, hyperreflexia, and incoordination occur, discontinuation of one or both agents should be considered.

Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported in patients receiving ZYVOX. In cases where the outcome is known, when ZYVOX was discontinued, the affected hematologic parameters returned to pretreatment levels. Complete blood counts should be monitored weekly, particularly in patients who receive ZYVOX for longer than 2 weeks.

ZYVOX is not approved and should not be used for the treatment of patients with catheter-related bloodstream infections or catheter-site infections.

ZYVOX has no clinical activity against Gram-negative pathogens and is not indicated for the treatment of Gram-negative infections. It is critical that specific Gram-negative therapy be initiated immediately if a concomitant Gram-negative pathogen is documented or suspected.

Clostridium difficile associated diarrhea has been reported with use of nearly all antibacterial agents, including ZYVOX, and may range in severity from mild diarrhea to fatal colitis.

Lactic acidosis has been reported with the use of ZYVOX. Patients receiving ZYVOX who develop recurrent nausea, vomiting, unexplained acidosis, or a low bicarbonate level should receive immediate medical evaluation.

Peripheral and optic neuropathy have been reported primarily in patients treated with ZYVOX for longer than the maximum recommended duration of 28 days. If patients experience symptoms of visual impairment, prompt ophthalmic evaluation is recommended.

Convulsions have been reported in patients treated with ZYVOX. In some of these cases, a history of seizures or risk factors for seizures was reported.

The most commonly reported adverse events in adults across phase 3 clinical trials were diarrhea, nausea, and headache.

IV/Oral
ZYVOX®
(linezolid)

SMART BUG. SMART DRUG.™

*Methicillin-resistant *Staphylococcus aureus*.

References: 1. Rubinstein E, Cammarata SK, Oliphant TH, Wunderink RG, and the Linezolid Nosocomial Pneumonia Study Group. Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: a randomized, double-blind, multicenter study. *Clin Infect Dis*. 2001;32:402-412. **2.** Wunderink RG, Cammarata SK, Oliphant TH, Kollef MH, for the Linezolid Nosocomial Pneumonia Study Group. Continuation of a randomized, double-blind, multicenter study of linezolid versus vancomycin in the treatment of patients with nosocomial pneumonia. *Clin Ther*. 2003;25:980-992. **3.** Wunderink RG, Rello J, Cammarata SK, Croos-Dabrera RV, Kollef MH. Linezolid vs vancomycin: analysis of two double-blind studies of patients with methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia. *Chest*. 2003;124:1789-1797.

Please see brief summary of prescribing information on adjacent page.