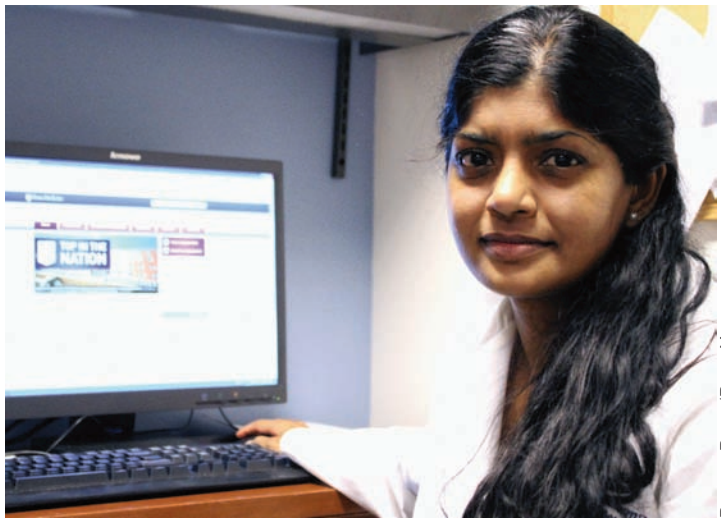
VOL. 8 • NO. 6 • JUNE 2013

CHEST Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS



ROBERT PRESS/PENN MEDICINE

Bringing in a new physician in the evening, rather than keeping the same one on call, could actually be a disruption to patient care, Dr. Meeta Prasad Kerlin's research found.

ICU outcomes no better with night intensivists

BY ALICIA AULT
IMNG Medical News

Having a critical care specialist physically present in the intensive care unit overnight does not seem to improve a broad range of patient outcomes, according to research published in the New England Journal of Medicine.

Dr. Meeta Prasad Kerlin and her colleagues at the University of Pennsylvania, Philadelphia, randomized admissions to a 24-bed medical ICU over a 1-year period; they offer several explanations as to why having a nighttime intensivist does not seem to make a difference. Their research was presented simultaneously at the annual meeting of the American Thoracic Society.

First, if the ICU is well staffed during the day and has adopted systems of care, there might not be a lot of room for patient improvement. Second, bringing on a new physician in the evening – rather than keeping the same intensivist on call – might disrupt continuity of care for some patients, they said.

All ICU patients admitted to the hospital at the university were randomized to the intervention group or the control group. The intervention group received care

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Shorter steroid treatment eased COPD exacerbations

Option offers short-, long-term benefits.

BY MARY ANN MOON
IMNG Medical News

In patients with acute COPD exacerbations, 5-day systemic glucocorticoid therapy was as effective as a conventional 14-day course of the drugs at preventing further exacerbations, according to a recent report in JAMA.

In a multicenter, randomized clinical trial, the 6-month rate of recurrent COPD exacerbation was 35.9% among patients who received the short course of systemic glucocorticoids, which was noninferior to the 36.8% rate among those who received the usual 2-week course, said Dr. Jörg D. Leuppi of the University Hospital of Basel (Switzerland) and his associates.

The short-term approach's main advantage is its significant reduction of patients' exposure to glucocorticoids, which in turn will likely decrease short-term adverse effects such as hyperglycemia, weight gain, increased blood pressure, and insomnia, the investigators said.

The short course also should prevent or delay longer-term steroid toxicities such as diabetes, osteoporosis, bone fractures, adrenal suppression, and

See **REDUCE** • *page 13*

Readmission penalties could double

BY MARY ELLEN SCHNEIDER
IMNG Medical News

The penalties are going up in Medicare's hospital readmission reduction program.

Starting on Oct. 1, hospitals could face up to a 2% cut in Medicare payments if their 30-day readmission rates for acute myocardial infarction, heart failure, and pneumonia are too high. The program started on Oct. 1, 2012, with a 1% cap on penalties.

The penalty increase was outlined in Medicare's proposed fiscal year 2014 inpatient prospective payment system rule released April 26.

The proposal also outlines the government's plans to expand the readmission reduction program to include two new readmission measures. Starting on Oct. 1, 2014, the

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INSIDE

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Have we come far enough in PAH patient outcomes?

CHANGEVI

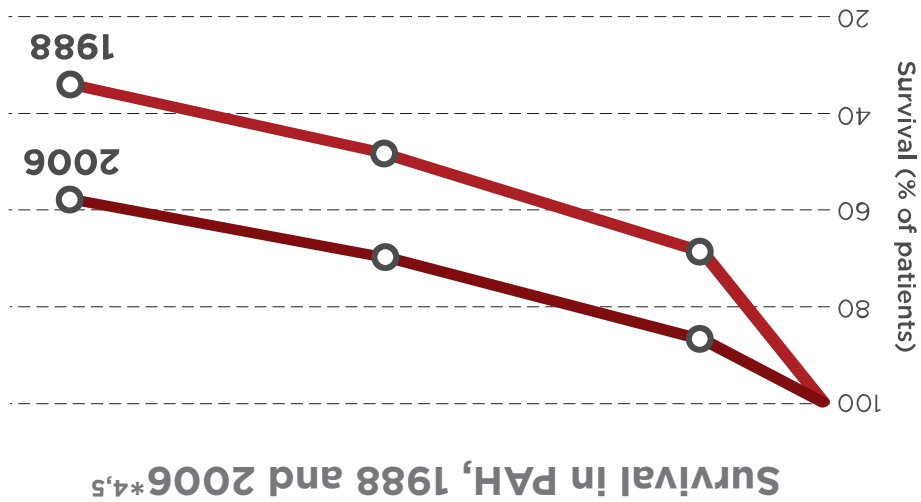
Despite advances, patients' long-term outcomes remain poor

Significant progress has been made in PAH treatment over the past 2 decades, yet patient morbidity and mortality remain high.[1] There is limited information on the long-term effects of PAH-specific therapies, and many patients continue to experience death, hospitalizations, and the need for additional therapies.[1,2]

Now is the time for a new perspective in PAH. Experts are calling for future PAH studies to deliver data on the long-term effect of therapy on clinical outcomes, such as hospitalizations and mortality.[1-3] Actelion is committed to investigating this evolving perspective in PAH.

References: 1. Galiè N, Manes A, Negro L, Palazzini M, Bacchi-Reggiani M, Branzi A. A meta-analysis of randomized controlled trials in pulmonary arterial hypertension. *Eur Heart J.* 2009;30:394-403. **2.** Gomberg-Maitland M, Dufton C, Oudiz RJ, Benza RL. Compelling evidence of long-term outcomes in pulmonary arterial hypertension? *J Am Coll Cardiol.* 2011;57:1053-1061. **3.** McLaughlin VV, Badesch DB, Delcroix M, et al. End points and clinical trial design in pulmonary arterial hypertension. *J Am Coll Cardiol.* 2009;54:S97-S107. **4.** Thenappan T, Shah SJ, Rich S, Gomberg-Maitland M. A USA-based registry for pulmonary arterial hypertension: 1982-2006. *Eur Respir J.* 2007;30:1103-1110. **5.** D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med.* 1991;115:343-349.

Survival in PAH, 1988 and 2006*[4,5]



*Survival observed over periods from 1981-1988 and 1982-2006, respectively.

ACTELION

PERSPECT

Ambrisentan may worsen pulmonary fibrosis

BY MARY ANN MOON
IMNG Medical News

The endothelin-receptor antagonist ambrisentan not only failed to benefit patients with idiopathic pulmonary fibrosis, it also may have facilitated disease progression in an international phase III clinical trial reported in Annals of Internal Medicine.

The trial was terminated early when an interim analysis of the data showed that patients treated with ambrisentan were more likely than control subjects receiving placebo to show progression of idiopathic pulmonary fibrosis (IPF) and to require more hospitalizations for respiratory indications, including acute IPF exacerbations and pneumonia. The findings were the same whether the study subjects had concomitant pulmonary hypertension.

"The observations in this study provide compelling evidence for ambrisentan as an ineffective treatment for patients with IPF and preclude further clinical evaluation of the drug as therapy for the disease. The data provide a basis for explicit guidance to clinicians not to use ambrisentan to treat patients with IPF, regardless of the presence of pulmonary hypertension," said Dr. Ganesh Raghu of the division of pulmonary and critical care medicine, University of Washington Medical Center, Seattle, and his associates.

The researchers undertook this large phase III study because preclinical data suggested that antagonism of endothelin receptors could lessen the severity of pulmonary fibrosis. And in a phase II study involving patients with a variety of interstitial lung diseases, a related endothelin antagonist, bosentan, had improved survival in the subgroup of patients with IPF.

Ambrisentan is a more selective endothelin A-receptor antagonist than bosentan and is currently approved for the treatment of pulmonary arterial hypertension. Dr. Raghu and his colleagues compared it against a matched placebo in 492 IPF patients treated at 136 clinical sites in North America, South America, Europe, Asia, New Zealand, and Australia.

When approximately 75% of the intended total enrollment of 660 patients was reached, an interim safety and efficacy analysis showed that the drug did not improve the primary endpoint, which was a composite of the time to disease progression, death from any cause, hospitalization for respiratory events, or a decrease in lung function. The trial sponsor, Gilead Sciences, terminated the study, and the findings were analyzed on the subjects enrolled up until that point.

The mean interval of exposure to ambrisentan (329 subjects) or placebo (163 subjects) was approximately 35 weeks. At baseline, patients in the active-treatment group and control group were similar regarding demographic traits, pulmonary hemodynamics, lung function, 6-minute walk distance, and quality of life.

Significantly more patients in the ambrisentan group (27.4%) than in the placebo group (17.2%) showed IPF progression. The active-treatment group also had significantly more respiratory hospitalizations (13.4% vs. 5.5%) and deaths (7.9% vs 3.7%) than did the control group, Dr. Raghu and his associates wrote (Ann. Intern. Med. 2013; 158:641-90).

However, there were no significant differences between the two study groups in the secondary endpoints of diffusion capacity for carbon monoxide; forced vital capacity; 6-minute walk distance; scores on the SF-36, which measures quality of life; or scores on the Transitional Dyspnea Index.

These findings were essentially the same when the data were analyzed according to whether or not patients had concomitant pulmonary hypertension at baseline. However, the subset of patients with pulmonary hypertension was small and not adequately powered to demonstrate a significant difference, so this finding should be interpreted with caution, the investigators said.

Regarding adverse events, significantly more patients taking ambrisentan than placebo reported dyspnea, worsening IPF, dizziness, and peripheral edema. Three times as many patients receiving ambrisentan (3%) dropped out of the study because of safety and tolerability issues, compared with those receiving placebo (1%).

This trial was supported by Gilead Sciences, which was involved in all aspects of the study.

VIEW ON THE NEWS

Dr. Marcos I. Restrepo, FCCP, comments: It looks as if, unfortunately, ambrisentan is not a possible future alternative to offer our patients with idiopathic pulmonary fibrosis due to the lack of clinical efficacy and associated poor clinical outcomes.

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CHEST PHYSICIAN

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POSTMASTER: Send change of address (with old mailing label) to CHEST PHYSICIAN, Subscription Service, 151 Fairchild Ave., Suite 2, Plainview, NY 11803-1709.

CHEST PHYSICIAN (ISSN 1558-6200) is published monthly for the American College of Chest Physicians by Frontline Medical Communications Inc., 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609. Subscription price is $230.00 per year. Phone 973-206-3434, fax 973-206-9378.

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Dupilumab cuts moderate, severe asthma exacerbations

BY MARY ANN MOON
IMNG Medical News

Dupilumab reduced exacerbations of moderate to severe asthma by 87% in adults with poorly controlled disease, and induced rapid and sustained improvements in numerous other measures of asthma severity in an industry-sponsored phase II study.

Dupilumab, a monoclonal antibody that inhibits interleukin-4 and interleukin-13 signaling, "showed substantial efficacy with regard to both objective and patient-reported end points" when it was used concomitantly with inhaled glucocorticoids and long-acting beta-agonists (LABAs), as well as when those background therapies were withdrawn, said Dr. Sally Wenzel of the University of Pittsburgh and her associates.

Dupilumab was associated with an 87% reduction in asthma exacerbation. Exacerbations occurred in 3 patients receiving dupilumab (6%) vs. 23 patients receiving placebo (44%).

"The magnitude and breadth of efficacy that we observed exceed those in other studies of Th2 [type 2 helper T-cell] cytokine inhibition," the researchers noted in a report in the New England Journal of Medicine that was presented simultaneously at the annual meeting of the American Thoracic Society.

Dupilumab currently is being assessed for the treatment of several diseases mediated by Th2 pathways. The goal of this phase II trial was to evaluate its safety and efficacy in adults with persistent moderate to severe asthma and elevated eosinophil levels whose symptoms were not well controlled with medium- to high-dose inhaled glucocorticoids plus LABAs (usually fluticasone and salmeterol).

The 104 participants were treated at 28 sites across the United States for 12 weeks, and then followed for another 8 weeks. During the intervention phase of the study, approximately half of the patients were randomized to receive once-weekly subcutaneous injections of dupilumab (300 mg) and half to receive matching placebo injections, in addition to the background asthma medications.

At week 4, the study subjects discontinued LABAs, and at weeks 6-9 they tapered off inhaled glucocorticoids. "This approach enabled us to observe the effects of dupilumab when added to background therapy, after LABA discontinuation, during the tapering of inhaled glucocorticoids, and as monotherapy," the researchers said.

The primary endpoint of the study was an asthma exacerbation during the 12-week intervention period. Exacerbations occurred in 3 patients receiving dupilumab (6%), compared with 23 receiving placebo (44%), a highly significant difference.

Continued on following page

Continued from previous page

In addition, the time to an asthma exacerbation was significantly longer with dupilumab than placebo. And forced expiratory volume in 1 second (FEV_1) "improved by more than 200 mL when dupilumab, as compared with placebo, was added to inhaled glucocorticoids and LABAs, an increase sustained during their tapering and discontinuation," the researchers noted (N. Engl. J. Med. 2013 May 21 [doi: 10.1056/NEJMoa1304048]).

Several other secondary endpoints also favored dupilumab over placebo, including morning peak expiratory flow values, scores on the Asthma Control Questionnaire (ACQ5), morning and evening asthma symptom scores, and the number of albuterol or levalbuterol inhalations needed per day. These measures improved at the beginning of the intervention in both study groups, then quickly returned to baseline levels in the placebo group while remaining constant in the dupilumab group.

The percentage of patients reporting adverse events was similar between the dupilumab and placebo groups (81% vs. 77%). These events tended to be nonspecific and mild, and included nasopharyngitis, nausea, and headache. One patient developed a progressive papular rash, urticaria, and edema after his ninth injection of dupilumab, which responded to nonurgent treatment of the symptoms and did not recur once the drug was withdrawn.

Forced expiratory volume in 1 second 'improved by more than 200 mL when dupilumab, as compared with placebo, was added to inhaled glucocorticoids and LABAs.'

No serious adverse events were attributed to the study drug, and no patient showed clinically significant changes in vital signs, findings on physical examination, laboratory tests, or ECGs.

"Further studies are needed to confirm these observations and better define the target population, dosing regimen, and long-term efficacy and safety," Dr. Wenzel noted.

However, the study findings support the theory that the Th2 cytokines interleukin-4 and interleukin-13 play a pathogenic role in persistent, moderate-to-severe asthma, she added.

This study was funded by Sanofi and Regeneron Pharmaceuticals. Dr. Wenzel reported ties to Sanofi, Regeneron, Amgen, Merck, and other companies. Her associates reported ties to numerous industry sources.

SABAs for exercise-induced bronchoconstriction

Guidelines warn of LABA side effects, advise adding an ICS or LTRA and nonpharmacologic measures.

BY ELIZABETH MECHCATIE
IMNG Medical News

Don't base diagnosis of exercise-induced bronchoconstriction on symptoms alone – but do have patients use inhaled short-acting beta-agonists and do warm-ups before exercise, according to new clinical practice guidelines issued by the American Thoracic Society.

The guidelines define exercise-induced bronchoconstriction (EIB) as "acute airway narrowing that occurs as a result of exercise."

Considering the high prevalence of EIB, which also affects people without asthma, "evidence-based guidelines for its management are of critical importance," said Dr. Jonathan Parsons, the lead author and chair of the committee that drafted the guidelines, in a statement.

The recommendations "synthesize the latest clinical evidence and will help guide the management of EIB in patients with or without asthma, and in athletes at all levels of competition," added Dr. Parsons, associate professor of internal medicine and associate director of the Ohio State University Asthma Center, Columbus.

A section on exercise, asthma, and doping – with reminders about which EIB drugs are banned in competitive sports (most beta-agonists) and which are allowed (short-acting inhaled albuterol and inhaled steroids) – is included in the guidelines.

The EIB guidelines, issued in May, cover pathogenesis, environmental triggers, diagnosis, treatment, and screening (Am. J. Resp. Crit. Care Med. 2013;187 [doi:10.1164/rccm.201303-0437ST]). Also included is a section on exercise, asthma, and doping – with reminders about which EIB drugs are banned in competitive sports (most beta-agonists) and which are allowed (short-acting inhaled albuterol and inhaled steroids).

Although the guidelines can apply both to adolescents and adults, they cannot be applied reliably to young children, Dr. Parsons noted in an interview.

EIB prevalence among people with asthma is not known, but the estimated prevalence among people who have not been diagnosed with asthma is as high as 20%, according to the ATS. EIB is more prevalent among athletes, affecting 30%-70% of Olympic and elite athletes. Environmental factors likely play a role, such as pollutants emitted from ice surfacing machines in indoor ice rinks, high trichloramine levels in the air of indoor pools, and cold, dry air.

Evidence-based guidelines for management of EIB 'are of critical importance.'

DR. PARSONS

An EIB diagnosis should not be based on symptoms, which are variable, nonspecific, and have poor predictive value. Instead, diagnosis should be made based on changes in lung function provoked by exercise, using serial lung function measurements after a specific exercise or a hyperpnea challenge. Assessing the effects of exercise on forced expiratory volume in 1 second (FEV_1) is preferred.

The guidelines grade EIB as mild, moderate, or severe, depending on the percent fall in FEV_1 from baseline. They also offer information on alternatives to exercise testing.

The authors rate pharmacologic and nonpharmacologic therapies based on the quality of the supportive evidence. Their first recommendation – administration of an inhaled short-acting beta-agonist (SABA) before exercise – earns a "strong" recommendation based on "high-quality" evidence. Patients typically take SABAs 15 minutes before exercise.

Because of the potential for serious side effects, the authors recommend against daily use of an inhaled long-acting beta-agonist (LABA) for EIB – a strong recommendation based on moderate-quality evidence.

For patients who use an inhaled SABA but continue to have symptoms or need to use the inhaled SABA "daily or more frequently," treatment options before exercise include a daily inhaled corticosteroid (ICS), a daily leukotriene-receptor antagonist, or a mast-cell–stabilizing agent.

"We generally add a daily inhaled ICS or a daily leukotriene-receptor antagonist first, with the choice between these agents made on a case-by-case basis depending upon patient preferences," the guideline authors note. Mast-cell–stabilizing agents and inhaled anticholinergic drugs "play a secondary role," they added. There is also a role for antihistamines in patient with continued symptoms despite treatment, but not for patients without allergies.

Nonpharmacologic measures include interval or combination warm-up exercises before planned exercise, which the guidelines recommend "for all patients" with EIB – a strong recommendation, based on moderate-quality evidence. The guidelines cite evidence showing a lower reduction in FEV_1 after exercise among people with EIB who engaged in "interval, low-intensity continuous; high-intensity continuous; or combination warm-up" before they exercised.

Another nonpharmacologic recommendation is use of a mask or another device that warms and humidifies the air when patients exercise in a cold climate.

While there is not much evidence supporting dietary modifications, patients interested in this approach can try a low-salt diet, or take fish oil or vitamin C supplements. However, the use of lycopene is not supported, based on the available evidence.

"Our overall recommendations regarding therapy leave a lot of options for the individual patient, which should be discussed with the patient's physician and tried and evaluated on an ongoing basis," the authors concluded.

The mainstay of treatment "remains maintaining good control of underlying asthma (if present) and preventing or treating symptoms of EIB with SABAs."

The EIB practice guidelines were supported by the ATS and approved by the ATS board of directors. Dr. Parsons' disclosures include having received lecture fees from AstraZeneca, GlaxoSmithKline, Merck, and Schering Plough. All but one of the other authors disclosed financial relations with a wide range of pharmaceutical companies.

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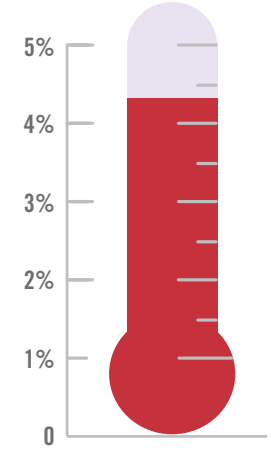
VIEW ON THE NEWS

Dr. Vera DePalo, FCCP, comments: The recent exercise-induced bronchoconstriction (EIB) guidelines presented by Dr. Parsons and his colleagues review the latest evidence on its pathogenesis, triggers, screening, diagnosis, and treatment. The recommendations are discussed in a concise question and answer format, and the guidelines include a diagnosis and treatment algorithm.

Guidelines are useful tools to help reduce variability in clinical care driving toward best practice. But it is important to review guidelines, practice strategies, and care standards as new evidence is available to ensure that current practice is based on the best available evidence.

DATA WATCH

Hot enough for you?



In a recent study, there was a 4.3% increase in respiratory admissions per 10°F rise in mean daily summer temperature for 1999-2008.

Note: Analysis included emergency hospitalizations for 12.5 million Medicare beneficiaries aged 65 years and older.

Source: Am. J. Respir. Crit. Care Med. 2013 March 13 (doi:10.1164/rccm.201211-1969OC) IMNG Medical Media

Fewer grads, more thoracic surgery board failures

Troubling trend in ABTS oral exam scores may reflect impact of decreased residency hours.

BY PATRICE WENDLING
IMNG Medical News

MINNEAPOLIS – The number of residents failing the American Board of Thoracic Surgery exams has risen significantly in the wake of reduced residency hours, a new study confirms.

The change is particularly alarming for the ABTS oral boards, Dr. Susan Moffatt-Bruce reported at the annual meeting of the American Association for Thoracic Surgery.

The failure rate for the oral exams doubled from 14.4% to 28.1% between 2000 to 2005 and 2006 to 2011, the 6 years before and 6 years after the Accreditation Council for Graduate Medical Education imposed an 80-hour residency work week. By 2012, 30% of residents were failing the oral exam.

Of the 903 residents who took the written exam between 2000 and 2005, 10.6% failed, compared with 17.4% of the 672 residents writing the exam between 2006 and 2007. By 2012, however, the success rate reached 85.4%.

Although the percentage failing the written exam was lower than for the oral exams in both time periods, it remained significantly higher from 2006 to 2011 than before the 80-hour work week requirement (12% vs. 21%) said Dr. Moffatt-Bruce, a cardiothoracic surgeon at the Ohio State Medical Center in Columbus.

"There are a decreasing number of trainees, and we will not meet the needs of a growing American population," she said, observing that the shortfall of certified cardiothoracic surgeons could be realized as early as 2020.

Dr. Moffatt-Bruce speculated that the higher failure rate for the oral exams could be the result of a decrease in the number of critical cardiac cases and in experiential learning for thoracic surgery residents, particularly on the weekends and evenings.

"It is very hard to pass an oral exam question about a scenario that you may never have encountered as a resident," she said.

Since 2000, the number of new certificates awarded by the ABTS has decreased steadily from a peak of 126 certificates in 2002 to 93 certificates in 2011. An additional 100 residents would need to be trained to meet the

Continued on following page

VITALS

Major finding: The failure rate for ABTS oral exams doubled from 14.4% to 28.1% between 2000-2005 and 2006-2011, the 6 years before and after the 80-hour residency work week.

Data source: Retrospective analysis of ABTS Board scores, both written and oral, from 2000 to 2011.

Disclosures: Dr. Moffatt-Bruce and her coauthors reported having no financial disclosures.

CMS penalties could double

Readmissions *from page 1*

program would also include readmissions associated with an acute exacerbation of chronic obstructive pulmonary disease, as well as readmissions for elective total hip or knee arthroplasty.

The inclusion of COPD for fiscal year 2015 was expected since that condition was specifically highlighted by Congress in the Affordable Care Act (ACA), which created the readmission reduction program. However, lawmakers had also recommended adding coronary artery bypass graft (CABG) surgery,

Among the quality measures considered in CMS' first domain are iatrogenic pneumothorax rate and postoperative pulmonary embolism or deep vein thrombosis rate.

percutaneous coronary intervention (PCI), and other vascular conditions, which are not included in the Centers for Medicare and Medicaid Services (CMS) proposal.

The fiscal 2014 payment proposal also includes a revised methodology for calculating hospital readmission rates in an effort to do a better job of accounting for certain planned readmissions.

The change is a mixed bag for hospitals, according to the Premier healthcare alliance. While the revised methodology will likely result in a more accurate payment calculation, it fails to take into consideration socioeconomic and community factors.

"Hospitals that serve high percentages of lower-income patients will be disproportionately penalized for circumstances outside their control," Blair Childs, senior vice president of public affairs at Premier, said in a statement. "This places additional financial burdens on already stressed local health care systems in these communities."

The Medicare program is also moving forward with the Hospital-Acquired Condition Reduction Program, also created by the ACA.

The new program, which begins on Oct. 1, 2014, levies a 1% penalty on hospitals that rank in the lowest-performing quartile for eight hospital-acquired conditions. The proposed rule includes the quality measures, scoring methodology, and correction process that are planned for the program.

During the first year, officials plan to use quality measures that are calculated using claims data or are part of the Inpatient Quality Reporting program. The eight measures are divided into two domains. Hospitals will receive a score for each measure, which will then be used to calculate a domain score. The two domains will be weighted equally to get a total score under the program, according to CMS.

The measures in the first domain are pressure ulcer rate; volume of foreign object left in the body; iatrogenic pneumothorax rate; postoperative physiologic and metabolic derangement rate; postoperative pulmonary embolism or deep vein thrombosis rate; and accidental puncture and laceration rate. CMS is also considering the use of a composite patient safety indicator measure set as an alternative to the first domain.

The second domain includes two health care–associated infection measures: central line–associated bloodstream infection and catheter-associated urinary tract infection.

CMS plans to account for risk factors such as age, gender, and comorbidities when calculating the measure rates.

There are no surprises in the conditions chosen for the new program, said Erik Johnson, senior vice president at Avalere Health. However, the fact that CMS officials chose to include eight measures at the start of the program indicates how serious they are about hospital-acquired conditions, he said.

Mr. Johnson predicted that hospitals will take these quality programs seriously as well. Through the combination of the hospital-acquired condition program, the readmission reduction program, value-based purchasing, and a few other programs, hospitals now have at least 7% of their Medicare payments at risk based on performance on quality measures, he said.

"It's already starting to move behaviors," Mr. Johnson said. "Hospitals are by and large making a good-faith effort to get better at all of those things. But there are going to be winners and losers, and the losers may end up losing big on a lot of this stuff."

CMS will accept public comments on the proposal until June 25 at www.regulations.gov. The agency is scheduled to release its final rule by Aug. 1.

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VIEW ON THE NEWS

Dr. Stuart M. Garay, FCCP, comments: CMS has chosen several approaches to help rein in hospital costs. Among them are the readmission reduction program and the hospital-acquired condition program. These programs, along with value-based purchasing, will place hospitals at risk for at least 7% of their Medicare payments – based on quality performance. COPD readmissions fall in the first program, while postop pulmonary embolism/deep vein thrombosis as well as iatrogenic pneumothorax place among hospital-acquired conditions.

Some of these conditions are preventable; others are not. Expect heat from your institution if things go bad. If they go well, maybe you will get a thank-you. Regardless, make sure your institution includes you in other potential gain-sharing programs that are being rolled out – and you might get more than a *thank-you*.

Continued from previous page

need for cardiothoracic surgeons by 2030, Dr. Moffatt-Bruce said.

She was careful to acknowledge existing efforts by various groups to attract students, such as the 6-year Integrated Cardiothoracic Surgery Residency Program (I-6), but she said additional strategies are needed to improve not only the number of trainees, but also the way in which they learn.

During a discussion of the results, Dr. Edward Verrier, surgical director, Joint Council of Thoracic Surgery Education, said various societies have gotten together and this spring will roll out a completely new content management system for the cardiothoracic surgery curriculum as well as a new curriculum and learning management tool that will help track issues related to competency and various milestones.

"It's very important to recognize that these issues have been on the table; they've been very carefully thought out at the board level, the society level and by some of the other organizations dedicated to education, and we will see significant transitions over the next year," he said.

Dr. Teresa Kieser, a cardiothoracic surgeon with University of Calgary in Canada, said that more than half of medical school graduates in Canada are women, but that perhaps women aren't choosing cardiothoracic surgery as a career.

Dr. Moffatt-Bruce, who trained in both the U.S. and Canada, agreed there are challenges facing women in cardiothoracic surgery, but said the curriculum needs to be more attractive to everyone and that providing experiences early on in the medical school curriculum and environment will entice residents "to see that this really is a great career choice, that this is the way of the future, and that the need is going to be very real.

"We have to set the burning platform for everyone and we can do that very easily as an association with the various societies."

pwendling@frontlinemedcom.com

VIEW ON THE NEWS

Dr. Lary Robinson, FCCP, comments: Dr. Susan Moffatt-Bruce and her colleagues have presented disturbing information about the training of cardiothoracic surgery residents, relating to the results on the American Board of Thoracic Surgery board examinations.

The oral examination in particular, which involves clinical case scenarios that reflect the fellow's experience in managing patients, has seen a dramatic increased failure rate as the residency workweek has declined, as required by the Accreditation Council for Graduate Medical Education (ACGME).

Less time in the hospital appears to equate to less experiential learning in patient care ... a logical conclusion that seems to be borne out by this study. And even more disturbing is the decline in the number of medical students being attracted into this specialty, which projects a significant future shortage of thoracic surgeons.

FDA approves once-daily combination for COPD

BY ELIZABETH MECHCATIE
IMNG Medical News

An inhaled powder formulation of the corticosteroid fluticasone furoate and vilanterol, a long-acting beta-2 agonist, has been approved by the Food and Drug Administration for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and/or emphysema.

It has also been approved to reduce chronic obstructive pulmonary disease (COPD) exacerbations in patients who have a history of exacerbations, according to a statement issued by the FDA.

In studies of 7,700 patients diagnosed with COPD, those treated with the inhaled corticosteroid/long-acting beta-2 agonist (ICS/LABA)

TOBI® PODHALER™ (tobramycin inhalation powder), for oral inhalation use
Initial U.S. Approval: 1975

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE
TOBI Podhaler is indicated for the management of cystic fibrosis patients with *Pseudomonas aeruginosa*.

Safety and efficacy have not been demonstrated in patients under the age of 6 years, patients with forced expiratory volume in 1 second (FEV_1) <25% or >80% predicted, or patients colonized with *Burkholderia cepacia* [see *Clinical Studies (14) in the full prescribing information*].

4 CONTRAINDICATIONS
TOBI Podhaler is contraindicated in patients with a known hypersensitivity to any aminoglycoside.

5 WARNINGS AND PRECAUTIONS

5.1 Ototoxicity
Caution should be exercised when prescribing TOBI Podhaler to patients with known or suspected auditory or vestibular dysfunction.

Ototoxicity, as measured by complaints of hearing loss or tinnitus, was reported by patients in the TOBI Podhaler clinical studies [see *Adverse Reactions (6.1)*]. Tinnitus may be a sentinel symptom of ototoxicity, and therefore the onset of this symptom warrants caution. Ototoxicity, manifested as both auditory (hearing loss) and vestibular toxicity, has been reported with parenteral aminoglycosides. Vestibular toxicity may be manifested by vertigo, ataxia or dizziness.

5.2 Nephrotoxicity
Caution should be exercised when prescribing TOBI Podhaler to patients with known or suspected renal dysfunction.

Nephrotoxicity was not observed during TOBI Podhaler clinical studies but has been associated with aminoglycosides as a class.

5.3 Neuromuscular Disorders
Caution should be exercised when prescribing TOBI Podhaler to patients with known or suspected neuromuscular dysfunction.

TOBI Podhaler should be used cautiously in patients with neuromuscular disorders, such as myasthenia gravis or Parkinson's disease, since aminoglycosides may aggravate muscle weakness because of a potential curare-like effect on neuromuscular function.

5.4 Bronchospasm
Bronchospasm can occur with inhalation of TOBI Podhaler [see *Adverse Reactions (6.1)*]. Bronchospasm should be treated as medically appropriate.

5.5 Laboratory Tests
Audiograms
Physicians should consider an audiogram at baseline, particularly for patients at increased risk of auditory dysfunction.

If a patient reports tinnitus or hearing loss during TOBI Podhaler therapy, the physician should refer that patient for audiological assessment.

Serum Concentrations
In patients treated with TOBI Podhaler, serum tobramycin concentrations are approximately 1 to 2 µg/mL one hour after dose administration and do not require routine monitoring. Serum concentrations of tobramycin in patients with known or suspected auditory or renal dysfunction or patients treated with a concomitant parenteral aminoglycoside (or other nephrotoxic or ototoxic medications) should be monitored at the discretion of the treating physician. If ototoxicity or nephrotoxicity occurs in a patient receiving TOBI Podhaler, tobramycin therapy should be discontinued until serum concentrations fall below 2 µg/mL.

The serum concentration of tobramycin should only be monitored through venipuncture and not finger prick blood sampling. Contamination of the skin of the fingers with tobramycin may lead to falsely increased measurements of serum levels of the drug. This contamination cannot be completely avoided by hand washing before testing.

Renal Function
Laboratory tests of urine and renal function should be conducted at the discretion of the treating physician.

5.6 Use in Pregnancy
Aminoglycosides can cause fetal harm when administered to a pregnant woman. Aminoglycosides cross the placenta, and streptomycin has been associated with several reports of total, irreversible, bilateral congenital deafness in pediatric patients exposed *in utero.* Patients who use TOBI Podhaler during pregnancy, or become pregnant while taking TOBI Podhaler should be apprised of the potential hazard to the fetus [see *Use in Specific Populations (8.1)*].

6 ADVERSE REACTIONS

6.1 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.

TOBI Podhaler has been evaluated for safety in 425 cystic fibrosis patients exposed to at least one dose of TOBI Podhaler, including 273 patients who were exposed across three cycles (6 months) of treatment. Each cycle consisted of 28 days on-treatment (with 112 mg administered twice daily) and 28 days off-treatment. Patients with serum creatinine ≥ 2 mg/dL and blood urea nitrogen (BUN) ≥ 40 mg/dL were excluded from clinical studies. There were 218 males and 207 females in this population, and reflecting the cystic fibrosis population in the U.S., the vast majority of patients were Caucasian. There were 221 patients ≥ 20 years old, 121 patients ≥ 13 to < 20 years old, and 83 patients ≥ 6 to < 13 years old. There were 239 patients with screening FEV_1 % predicted ≥ 50%, 156 patients with screening FEV_1 % predicted < 50%, and 30 patients with missing FEV_1 % predicted.

The primary safety population reflects patients from Study 1, an open-label study comparing TOBI Podhaler with TOBI (tobramycin inhalation solution, USP) over three cycles of 4 weeks on treatment followed by 4 weeks off treatment. Randomization, in a planned 3:2 ratio, resulted in 308 patients treated with TOBI Podhaler and 209 patients treated with TOBI. For both the TOBI Podhaler and TOBI groups, mean exposure to medication for each cycle was 28-29 days. The mean age for both arms was between 25 and 26 years old. The mean baseline FEV_1 % predicted for both arms was 53%.

Table 1 displays adverse drug reactions reported by at least 2% of TOBI Podhaler patients in Study 1, inclusive of all cycles (on and off treatment). Adverse drug reactions are listed according to MedDRA system organ class and sorted within system organ class group in descending order of frequency.

Table 1: Adverse reactions reported in Study 1 (occurring in ≥2% of TOBI Podhaler patients)

Primary System Organ Class Preferred Term	TOBI Podhaler N=308 %	TOBI N=209 %
Respiratory, thoracic, and mediastinal disorders		
Cough	48.4	31.1
Lung disorder[1]	33.8	30.1
Productive cough	18.2	19.6
Dyspnea	15.6	12.4
Oropharyngeal pain	14.0	10.5
Dysphonia	13.6	3.8
Hemoptysis	13.0	12.4
Nasal congestion	8.1	7.2
Rales	7.1	6.2
Wheezing	6.8	6.2
Chest discomfort	6.5	2.9
Throat irritation	4.5	1.9
Gastrointestinal disorders		
Nausea	7.5	9.6
Vomiting	6.2	5.7
Diarrhea	4.2	1.9
Dysgeusia	3.9	0.5
Infections and infestations		
Upper respiratory tract infection	6.8	8.6
Investigations		
Pulmonary function test decreased	6.8	8.1
Forced expiratory volume decreased	3.9	1.0
Blood glucose increased	2.9	0.5
Vascular disorders		
Epistaxis	2.6	1.9
Nervous system disorders		
Headache	11.4	12.0
General disorders and administration site conditions		
Pyrexia	15.6	12.4
Musculoskeletal and connective tissue disorders		
Musculoskeletal chest pain	4.5	4.8
Skin and subcutaneous tissue disorders		
Rash	2.3	2.4

[1]This includes adverse events of pulmonary or cystic fibrosis exacerbations

Adverse drug reactions that occurred in <2% of patients treated with TOBI Podhaler in Study 1 were: bronchospasm (TOBI Podhaler 1.6%, TOBI 0.5%); deafness including deafness unilateral (reported as mild to moderate hearing loss or increased hearing loss) (TOBI Podhaler 1.0%, TOBI 0.5%); and tinnitus (TOBI Podhaler 1.9%, TOBI 2.4%).

Discontinuations in Study 1 were higher in the TOBI Podhaler arm compared to TOBI (27% TOBI Podhaler vs 18% TOBI). This was driven primarily by discontinuations due to adverse events (14% TOBI Podhaler vs 8% TOBI). Higher rates of discontinuation were seen in subjects ≥ 20 years old and those with baseline FEV_1 % predicted < 50%.

Respiratory related hospitalizations occurred in 24% of the patients in the TOBI Podhaler arm and 22% of the patients in the TOBI arm. There was an increased new usage of antipseudomonal medication in the TOBI Podhaler

combination "showed improved lung function and reduced exacerbations compared to placebo," the statement said.

The fixed-dose combination of 100 mcg of fluticasone furoate with 25 mcg of vilanterol is formulated in a dry powder. It is administered once a day in a new inhaler that provides 30 doses, according to GlaxoSmithKline, which developed the product with Theravance.

The product will be marketed as Breo Ellipta.

As with other LABAs, the prescribing information for this product includes a boxed warning about the risk of asthma-related deaths, although it is not approved for treating asthma.

Nasopharyngitis, oral candidiasis, headache, and upper respiratory tract infections were among the most common side effects reported by patients using the product, according to the FDA.

The approval was announced May 10, less than a month after the majority of the FDA's Pulmonary-Allergy Drugs Advisory Committee voted to support approval of the product for long-term maintenance treatment of airflow obstruction and reducing COPD exacerbations. The panel nearly unanimously agreed that the treatment had "clinically meaningful" benefit as a long-term maintenance treatment for airflow obstruction They voted 8-5 that the data provided "substantial evidence" that reductions in exacerbations were clinically meaningful.

The two inhaled ICS/LABA treatments approved by the FDA for COPD are the combination of fluticasone propionate and salmeterol (Advair Diskus), also marketed by GSK, and the combination of budesonide and formoterol (Symbicort). Both are administered twice a day. Salmeterol and formoterol are both available as separate products to treat COPD. Vilanterol, which is the LABA component of Breo Ellipta, will not be available separately.

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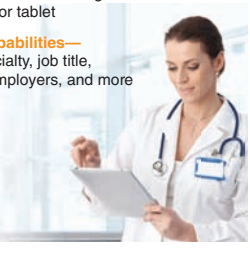
VIEW ON THE NEWS

Dr. Darcy D. Marciniuk, FCCP, comments: While not a new pharmacologic class, clinicians now have another effective inhaled combination product that differs in its device and once-a-day dosing. Shown to significantly improve lung function and reduce exacerbations in patients suffering from COPD, the differences compared with existing formulations should be appreciated.



Ultralow-dose CT bests x-ray for lung cancer follow-up

BY PATRICE WENDLING
IMNG Medical News

MINNEAPOLIS – Minimal-dose computed tomography was superior to chest radiographs for surveillance after curative lung cancer resection in a randomized controlled trial involving over 300 patients.

"Minimal-dose CT should be the modality of choice for surveillance after resection of lung cancer," Dr. Waël Hanna said at the annual meeting of the American Association for Thoracic Surgery.

Repeated radiation exposure and a high false-positive rate have been stumbling blocks to national lung cancer screening with low-dose spiral CT, despite the technology demonstrating 20% fewer lung cancer deaths compared with chest x-ray in asymptomatic heavy smokers in the National Lung Cancer Screening Trial (NLST). Minimal-dose CT of the chest delivers a radiation dose of 0.2 mSv per scan, which is comparable to chest x-ray at 0.16 mSv and lower than a diagnostic CT or low-dose CT at roughly 8 mSv and 1.5 mSv, he said.

The 311 patients in the current study were prospectively enrolled after curative resection and underwent minimal-dose CT and chest x-ray at 3, 6, 12, 18, 24, 36, 48, and 60 months. A total of 1,137 pairs of chest x-ray and CT scans were analyzed by radiologists blinded to the other modality.

Minimal-dose CT detected 94.2% of the new or recurrent lung cancer, compared with 21.1% for chest x-ray (*P* value .0001), said Dr. Hanna, a thoracic surgery fellow at the University of Toronto.

The increased sensitivity came at a cost of significantly lower specificity (86% vs. 99.9%) and positive predictive value (251% vs. 91.6%; both *P* less than .0001). The negative predictive value for minimal-dose CT, however, was almost perfect (99.7% vs. 96.1%; $P = .007$).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Dr. Waël Hanna: Minimal-dose CT detected 94.2% of new or recurrent cancer.

More importantly, of the 63 patients diagnosed with new or recurrent cancer, 49 (78%) had asymptomatic disease detected only on minimal-dose CT, Dr. Hanna said. Two-thirds of the asymptomatic patients were diagnosed within the first year of surveillance and 94% within 2 years of initial surgery.

"Why is this important? Because when you find it at an earlier stage, earlier in time, you can do something about it," he said.

Asymptomatic patients who were restaged and given curative surgery or radiation went on to live a median of 69 months (range, 12-76) after the initial operation, compared with a median survival of 25 months (range, 6-48) among asymptomatic patients given palliative treatment after restaging (*P* less than .001).

The 14 patients with symptomatic recurrent or new cancer had a median survival of only 15 months (range, 7-63) with palliative care.

"We are not saying that minimal-dose CT improves survival because these two patient populations are different," Dr. Hanna said. "The patient who presents with asymptomatic disease of the chest and is a candidate for surgery is clearly different from the patient who presents with brain metastases and is symptomatic. But follow-up with minimal-dose CT allows us to identify this cohort of patients in whom close surveillance after surgery is not futile, in whom close surveillance after surgery is amenable to intervention and treatment, and is associated with long survival."

Several prominent guidelines, including those from the AATS and National Comprehensive Cancer Network, have moved to include regular CT scans in the wake of the NLST, but evidence is lacking to suggest that earlier treatment of recurrence leads to better outcomes.

Dr. Michael Jaklitsch, an invited discussant from Brigham and Women's Hospital, Boston, said that the investigators were able to take a group of patients who would have had a 5-year survival of 50% and raise it to 75% through aggressive surveillance and show that they were "truly curing" these patients.

"Is this enough data to change our personal practices today," he posited. "For me personally, the answer is yes. This single paper presents me with enough data to say I will use minimal-dose CT scan as my sole method of screening for recurrence of early-stage lung cancer moving forward."

Dr. Jaklitsch questioned whether there were subpopulations in whom minimal-dose CT would not work, like the obese or those with surgical clips. Dr. Hanna said that radiologists at his center are more comfortable using low-dose CT for surveillance because of the risk of scatter in either of these subgroups or in those with mediastinal involvement.

Dr. Hanna also noted that minimal-dose CT is not available everywhere, but Dr. Jaklitsch said that he took the specifications from the paper to his community hospital and they said they could be done. "So at least in the U.S., this will have dramatic penetrance," he added.

Dr. Hanna and his coauthors reported having no study sponsorship or financial disclosures.

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VIEW ON THE NEWS

Dr. W. Michael Alberts, FCCP, comments: It is important to remember that screening for a primary lung cancer is a different procedure than conducting surveillance for a recurrence or a second primary lung cancer. The pretest probability of discovering a cancer in these two situations is likely different and therefore plays a role in evaluating the summary statistics.

COMMENTARY: Stopping low-dose ICS use poses risks

BY JON O. EBBERT, M.D.
IMNG Medical News

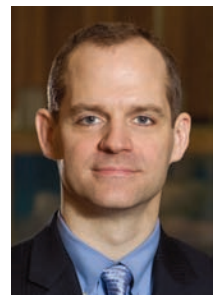
A significant dissatisfier for both clinician and patient is that inhaled corticosteroids, commonly underutilized and potentially lifesaving medications, are almost never (if ever) covered at the lowest tier by insurance companies.

We would select a first-tier medication if there were one that we could substitute for an ICS; but frequently there isn't, so we can't.

Because of this, patients may be financially motivated to simply stop the medication – especially if they perceive that they are on the lowest doses and believe the medication perhaps is not needed at all.

Clinicians, meanwhile, are doing the balancing act of moving patients to the lowest doses in order to avoid side effects while maintaining optimal disease control.

So, what are the risks when patients stop using inhaled corticosteroids?


DR. EBBERT

Dr. Matthew A. Rank of the Mayo Clinic, Rochester, Minn., and his colleagues recently published a systematic review of the literature to answer this question (J. Allergy Clin. Immunol. 2013;131:724-9).

In this review, randomized, controlled clinical trials in which the study intervention was continuing or stopping low-dose ICSs were included. Studies had to have 4 or more weeks of a run-in with stable doses of ICSs to ensure a minimum period of asthma stability. Seven studies met inclusion criteria. Two studies were exclusively in children, and one was exclusively in adults.

Asthma exacerbations were more likely among patients who stopped ICSs, compared with those who did not (relative risk, 2.35; 95% CI: 1.88-2.92). The risk for an asthma exacerbation in the next 6 months on low-dose ICSs was 16% if patients continued taking the medications, and 38% if they stopped.

For every five patients who stopped ICSs, one patient would be expected to have an asthma exacerbation in the next 6 months – which could have been prevented if steroids had been continued.

The mean decrease in forced expiratory volume in 1 second associated with discontinued ICS use was 130 mL.

Most patients can step down with ICSs if they are on long-acting beta-agonists. Expert panels have suggested that patients should be controlled for 3 months before stepping down therapy. Findings from this study further suggest that patients who discontinue low-dose ICSs are at an increased risk of asthma exacerbation.

We need to help our patients understand the risk of stopping low-dose ICSs and encourage them, as much as they are able, to stay on them.

Dr. Ebbert is professor of medicine and a primary care clinician at the Mayo Clinic in Rochester, Minn. He reported having no relevant financial conflicts. The opinions expressed are those of the author.

5-day steroids ease COPD flares

REDUCE *from page 1*

ocular complications.

The investigators performed the noninferiority trial, known as the REDUCE (Reduction in the Use of Corticosteroids in Exacerbated COPD) study, because no adequately powered, randomized clinical trial has compared directly the outcomes of these two treatment durations. Despite that, "it has become quite common clinical practice to administer glucocorticoids in COPD exacerbations for shorter periods," the study authors noted.

The REDUCE trial's results were published online and simultaneously reported at the annual meeting of the American Thoracic Society.

The study included 311 consecutive patients who presented with COPD exacerbations to emergency departments at five Swiss teaching hospitals during a 5-year period. All patients were older than 40 years, were current or past smokers, and had a smoking history of 20 or more pack-years (JAMA 2013 May 21 [doi:10.1001/jama.2013.5023]).

All the study subjects received 40 mg of IV methylprednisolone on day 1, followed by 40 mg of oral prednisone on days 2-5. On days 6-14, 155 patients were randomly assigned to continue receiving oral prednisone (conventional therapy) and 156 to receive a matching placebo (short-course therapy). Patients, caregivers, and researchers were blinded to group assignment.

All the patients also received a broad-spectrum antibiotic for 7 days to prevent pneumonia; nebulized short-acting bronchodilators as needed while hospitalized; inhaled glucocorticoids combined with an inhaled beta-agonist twice daily; and inhaled tiotropium once daily. They all also received physiotherapy, supplemental oxygen, and ventilatory support according to accepted guidelines.

Patients who received short-course glucocorticoid therapy had a median cumulative prednisone dose of 200 mg and a mean cumulative dose of 379 mg. In contrast, those who received a longer duration of treatment had a median cumulative prednisone dose of 560 mg and a mean cumulative dose of 793 mg.

After 180 days of follow-up, 56 (35.9%) patients in the short-course therapy group and 57 (36.8%) in the conventional therapy group reached the primary endpoint of a recurrent COPD exacerbation. The time to recurrence did not differ between the two groups.

In addition, the hazard ratios for experiencing a recurrence were nearly identical between the two study groups in both an intention-to-treat analysis and a per-protocol analysis, "meeting our noninferiority criterion," Dr. Leuppi and his colleagues said.

The findings remained robust in sensitivity analyses that adjusted for variables such as patient age and sex. They also persisted in subgroup analyses that compared patients who had different severities of underlying COPD and different past histories of glucocorticoid use.

Overall survival was not significantly different between patients who received 5 days and those who received 14 days of systemic glucocorticoids. The short-course group also showed no increase in the need for mechanical ventilation while hospitalized.

Measures of forced expiratory volume in 1 second improved significantly in both groups by day 6 and remained stable thereafter, with "almost no differences" between groups. Patients in both groups reported significantly ameliorated dyspnea, as well as similarly improved bronchitis-related quality of life and overall performance.

Regarding short-term adverse effects of exposure to glucocorticoids, rates of new or worsening hypertension and new or worsening hyperglycemia were comparable between the two study groups. "We surmise that the length of hospital stay was insufficient to detect significant differences in blood pressure and blood glucose levels between groups, because these glucocorticoid adverse effects do not develop immediately after initiation of treatment," the researchers said.

There also were no differences in longer-term toxicities such as rates of infection, gastrointestinal bleeding, insomnia, fractures, psychiatric symptoms, or heart failure.

A surprising finding was that patients who received short-term glucocorticoids had a significantly shorter hospital stay (median, 8 days) than did those who received conventional glucocorticoids (median, 9 days). "Because we did not observe significant differences in glucocorticoid-related, short-term adverse effects, we cannot readily explain this observation, which might be a chance finding," Dr. Leuppi and his associates said.

This study was supported by the University Hospital Basel, the Hospital Center of Biel-Bienne, AstraZeneca, and several research foundations. The researchers reported ties to industry sources.

VIEW ON THE NEWS

Dr. Marcos I. Restrepo, FCCP, comments: This interesting study challenged the duration of systemic glucocorticoid therapy in patients with acute COPD exacerbations (AECOPD). A short course (5 days) of corticosteroids was as effective in preventing recurrent AECOPD when compared with a longer course (14 days) of corticosteroid therapy.

Studies like this, that assess the duration of corticosteroids, antimicrobials, and other risky therapies, are welcome and needed in order to improve patient safety and prevent unnecessary exposure to medications.

Can you tell which patient has ALK-positive NSCLC?

Molecular testing is increasingly important in lung cancer

In a study of 420 patients with adenocarcinoma non-small cell lung cancer (NSCLC), more than 50% of tumors tested positive for a predictive biomarker.[1] About 3% to 5% of patients with advanced NSCLC harbor a genetic alteration known as the anaplastic lymphoma kinase (*ALK*) fusion gene.[2-9] The *ALK* fusion gene (a fusion between *ALK* and other genes such as *EML4*) is believed to be a key oncogenic driver that contributes to cell proliferation and tumor survival.[6,10-12]

Approval of the first ALK inhibitor is a compelling reason to test patients for the *ALK* fusion gene

XALKORI® (crizotinib)—**the first ALK inhibitor**—may offer antitumor activity for patients with locally advanced or metastatic ALK-positive NSCLC. As an inhibitor of the ALK receptor tyrosine kinase, XALKORI is believed to block growth and survival mechanisms in tumor cell lines, potentially leading to regression or stabilization of tumors.[7] Testing is necessary to identify patients for whom XALKORI may be appropriate. An FDA-approved test must be used to determine which patients have ALK-positive NSCLC.

Clinical characteristics should not be used to determine which patients to test[13]

In XALKORI registration studies, the *ALK* fusion gene was identified in patients who varied by age, race, gender, and performance status. While the *ALK* fusion gene was identified more frequently in never-smokers, it was also seen in former and current smokers. In addition, the *ALK* fusion gene was identified more frequently in patients with adenocarcinoma but occurred in all histologic types.

Thus, simultaneous testing for all clinically relevant biomarkers—including ALK—prior to treatment initiation may help guide therapeutic decisions.[14]

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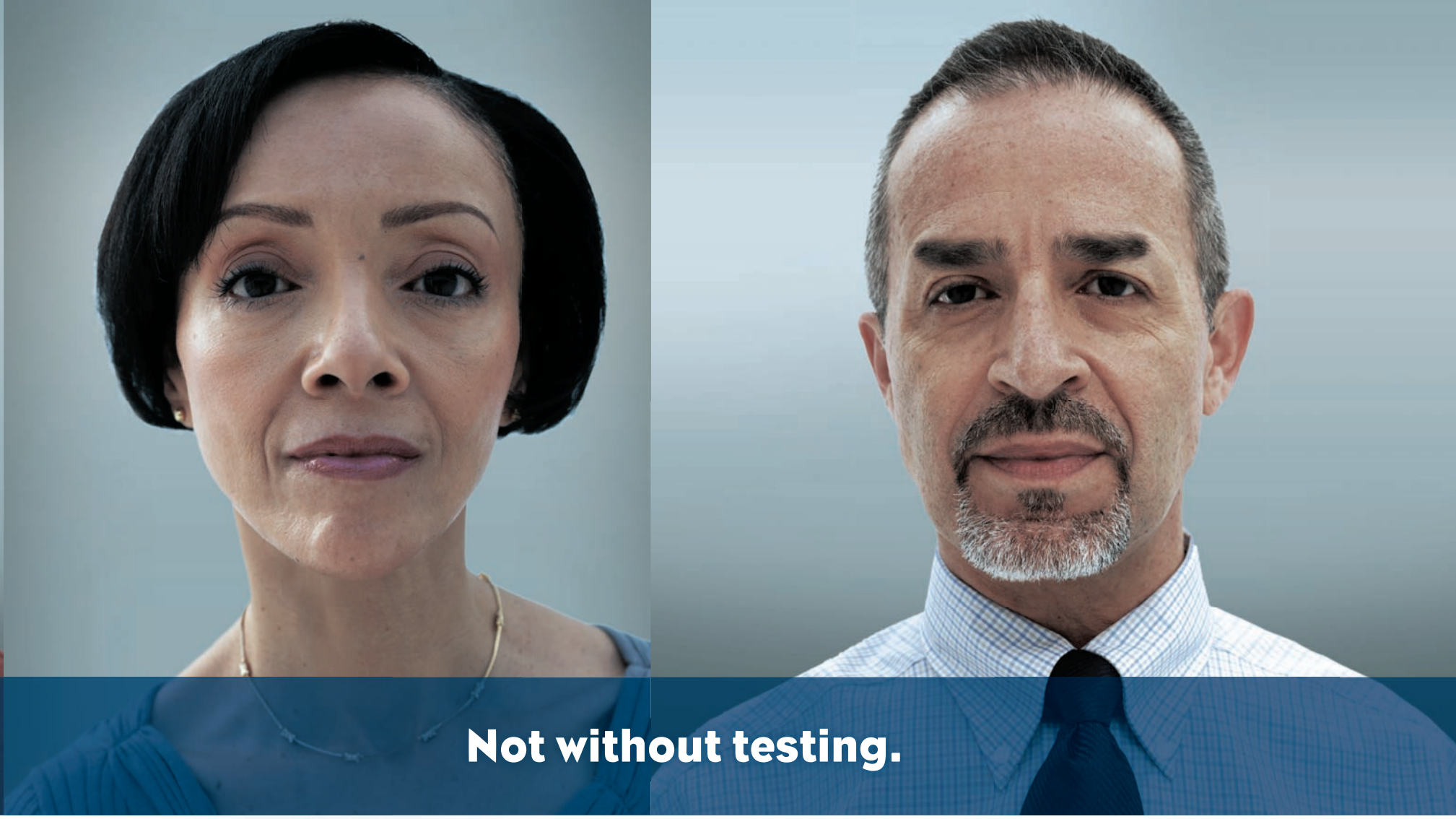

The National Comprehensive Cancer Network® (NCCN®) recommends that all patients with advanced or metastatic NSCLC determined by histology to be nonsquamous or NOS undergo EGFR and ALK testing[13]

- EGFR and ALK testing is also recommended in patients with squamous cell carcinoma if they never smoked and if small biopsy specimens were used to assess histology

XALKORI** is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test. This indication is based on response rate. There are no data available demonstrating improvement in patient reported outcomes or survival with* **XALKORI.

SELECTED SAFETY INFORMATION

Drug-induced hepatotoxicity with fatal outcome has occurred. Transaminase elevations generally occurred within the first 2 months of treatment. Monitor with liver function tests including ALT and total bilirubin once a month and as clinically indicated, with more frequent repeat testing for increased liver transaminases, alkaline phosphatase, or total bilirubin in patients who develop transaminase elevations. Temporarily suspend, dose reduce, or permanently discontinue XALKORI as indicated.

XALKORI has been associated with severe, life-threatening or fatal treatment-related pneumonitis in clinical trials with a frequency of 4 in 255 (1.6%) patients. All of these cases occurred within 2 months after the initiation of treatment. Monitor patients for pulmonary symptoms indicative of pneumonitis. Exclude other causes and permanently discontinue XALKORI in patients with treatment-related pneumonitis.

Detection of ALK-positive NSCLC using an FDA-approved test, indicated for this use, is necessary for selection of patients for treatment with XALKORI.

Please see additional Important Safety Information on the next page and accompanying brief summary of Prescribing Information.

For more information, please visit **www.xalkorihcp.com**.

Pfizer Oncology

250 MG CAPSULES
XALKORI®
CRIZOTINIB

XALKORI® (crizotinib) is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test.

This indication is based on response rate. There are no data available demonstrating improvement in patient reported outcomes or survival with XALKORI.

IMPORTANT SAFETY INFORMATION

Hepatotoxicity: Drug-induced hepatotoxicity with fatal outcome has occurred. Transaminase elevations generally occurred within the first 2 months of treatment. Monitor with liver function tests including ALT and total bilirubin once a month and as clinically indicated, with more frequent repeat testing for increased liver transaminases, alkaline phosphatase, or total bilirubin in patients who develop transaminase elevations. Temporarily suspend, dose reduce, or permanently discontinue XALKORI as indicated.

Pneumonitis: XALKORI has been associated with severe, life-threatening, or fatal treatment-related pneumonitis in clinical trials with a frequency of 4 in 255 (1.6%) patients. All of these cases occurred within 2 months after the initiation of treatment. Monitor patients for pulmonary symptoms indicative of pneumonitis. Exclude other causes and permanently discontinue XALKORI in patients with treatment-related pneumonitis.

QT Interval Prolongation: QTc prolongation has been observed. Avoid use of XALKORI in patients with congenital long QT syndrome. Consider periodic monitoring with electrocardiograms (ECGs) and electrolytes in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or who are taking medications that are known to prolong the QT interval. Permanently discontinue XALKORI for grade 4 QTc prolongation. XALKORI should be withheld for grade 3 QTc prolongation until recovery to ≤ grade 1. Permanently discontinue XALKORI if grade 3 QTc prolongation recurs.

ALK Testing: Detection of ALK-positive NSCLC using an FDA-approved test, indicated for this use, is necessary for selection of patients for treatment with XALKORI.

Pregnancy: XALKORI can cause fetal harm when administered to a pregnant woman based on its mechanism of action. Women of childbearing potential should be advised to avoid becoming pregnant while receiving XALKORI. If the patient or their partner becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus.

Adverse Reactions: Among the 397 patients for whom information on deaths and serious adverse reactions is available, deaths within 28 days of the last dose of study drug occurred in 45 patients. Ten (2.5%) patients died within 28 days of their first dose of study drug. Causes of death included disease progression (32 patients), respiratory events (9), and other (4).

Safety of XALKORI was evaluated in 255 patients with locally advanced or metastatic ALK-positive NSCLC in 2 single-arm clinical trials (Studies A and B). The most common adverse reactions (≥25%) across both studies were vision disorder, nausea, diarrhea, vomiting, edema, and constipation. Grade 3-4 adverse reactions in ≥4% of patients in both studies included ALT increased and neutropenia.

- Vision disorders including visual impairment, photopsia, vision blurred, vitreous floaters, photophobia, and diplopia were reported in 159 (62%) patients in clinical trials. Consider ophthalmological evaluation, particularly if patients experience photopsia or experience new or increased vitreous floaters. Severe or worsening vitreous floaters and/or photopsia could also be signs of a retinal hole or pending retinal detachment. Advise patients to exercise caution when driving or operating machinery due to the risk of developing a vision disorder.
- Neuropathy attributed to study drug was reported in 34 (13%) patients. Grade 2 motor neuropathy and grade 3 peripheral neuropathy were reported in 1 patient each.
- Bradycardia was reported in 12 (5%) patients treated with XALKORI. All of these cases were grade 1 or 2 in severity.
- Complex renal cysts were reported in 2 (1%) patients treated with XALKORI. There were no reports of abnormal urinalyses or renal impairment in these cases.

Grade 3 or 4 laboratory abnormalities of neutropenia, thrombocytopenia, and lymphopenia were observed in 5.2%, 0.4%, and 11.4% of patients, respectively.

Drug Interactions: Exercise caution with concomitant use of moderate CYP3A inhibitors. Avoid grapefruit or grapefruit juice which may increase plasma concentrations of crizotinib. Avoid concomitant use of strong CYP3A inducers and inhibitors. Dose reduction may be needed for coadministered drugs that are predominantly metabolized by CYP3A.

Nursing Mothers: Given the potential for serious adverse reactions in nursing infants, consider whether to discontinue nursing or discontinue XALKORI.

Hepatic Impairment: XALKORI has not been studied in patients with hepatic impairment. As crizotinib is extensively metabolized in the liver, hepatic impairment is likely to increase plasma crizotinib concentrations. Use caution in patients with hepatic impairment.

Renal Impairment: No starting dose adjustment is needed for patients with mild and moderate renal impairment. No data are available for patients with end-stage renal disease. Use caution in patients with severe renal impairment or patients with end-stage renal disease.

Please see accompanying brief summary of Prescribing Information.

For more information, please visit **www.xalkorihcp.com**.

250 MG CAPSULES
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Pfizer Oncology CRI550916-01

Printed in USA/March 2013

Viral test cut antibiotic use for respiratory illness

BY MICHELE G. SULLIVAN
IMNG Medical News

WASHINGTON – A rapid viral testing panel decreased the odds of inappropriate antibiotic use by 67% in children hospitalized with acute respiratory illness, allowing 6% of the children to discontinue use.

The test could be part of a facility's overall antibiotic control program, Dr. Russell McCulloh said at the annual meeting of the Pediatric Academic Societies.

"There is always a strong possibility for a bacterial coinfection in these patients, and that can be very hard to determine because we don't have a gold standard test," he said. Adjunctive diagnostic testing is needed to "close the loop and implement this as part of an antibiotic stewardship program," said Dr. McCulloh, an infectious disease specialist at Rhode Island Hospital, Providence.

He conducted a chart review of 1,731 children admitted to the hospital for acute respiratory illness from 2009 to 2011, comparing rates of antimicrobial use in those who had the rapid viral panel (809) and those who did not (922). A total of 860 had received antibiotics before having the test; 255 had received oseltamivir.

Most of the children who had a positive viral panel were prescribed oseltamivir (87%); the drug was used in 18% of those who had a negative test. In a multivariate analysis, a positive rapid viral panel was the single biggest predictor of getting the antiviral drug, increasing the odds by more than 27 times, Dr. McCulloh said.

Younger age had a significant association, but the odds ratio was 1.7. Having a significant past medical history was predictive in an unadjusted analysis, but not in the final model.

Antibiotics were given to 11% of children who had the viral testing, but to 100% of those who did not have it, Dr. McCulloh said. Antibiotics were used in 51% of those with a positive test, and 67% of those with a negative test. Antibiotics were discontinued in 6% of children who had a positive viral test.

A multivariate analysis found several factors significantly associated with antibiotic use. A significant past medical history increased the odds by 7%. Stronger predictors included a codiagnosis of acute otitis media (OR, 6.0), an abnormal chest x-ray (OR, 2.57), and a positive blood culture (OR, 3). However, a negative viral panel was associated with a 69% decreased chance of receiving an antibiotic.

Dr. McCulloh had no disclosures.

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VIEW ON THE NEWS

Dr. Susan Millard, FCCP, comments: It would be helpful to know what type of rapid viral panel was used and what it included. Also, even though it is a retrospective study, it is interesting to review these types of studies to help guide future pediatric community-acquired pneumonia (CAP) protocols.

Night intensivist benefit questioned

Outcomes *from page 1*

from an intensivist (a board-eligible or board-certified critical care specialist) who was on staff from 7 p.m. to 7 a.m., or from residents who normally were assigned to the ICU.

The control group received care from residents, who were able to reach two daytime intensivists or two critical care fellows at night by phone. Generally, the nursing ratio was one per two patients.

The nighttime intensivists were daytime staff who volunteered to take on a nighttime assignment. During the study, they covered one night a week.

Overall, 820 patients were assigned to the intervention (4 were later excluded due to missing data), and 778 were in the control group (7 ended up with missing data). In total, 175 nights were assigned to the intervention; 95% (166) of those nights were staffed by an intensivist.

The median age of patients was 60 years, and about half were men. Almost half were admitted from the emergency department, while just over a third were transferred from the hospital's general floor. The median APACHE (Acute Physiology and Chronic Health Evaluation) III score was 67 (doi: 0.1056/NEMJoa1302854).

Sixty-one percent (970) of all patients were admitted to the ICU at night (5 p.m. to 5 a.m.). Overall, 381 patients (24%) died in the hospital, with 293 (18%) of them dying in the ICU.

The authors found no effect on length of stay in the ICU (median, 52.7 hours) for those in the intervention group. They calculated a "rate ratio," which was the rate of instantaneous discharge from the ICU in the intervention group divided by the rate of instantaneous discharge from the ICU in the control group. For ICU length of stay, the ratio was 0.98 ($P = .72$); a ratio of more than 1 would mean that the intervention shortened the time to discharge.

They found similar ratios for hospital length of stay (median, 174 hours in the intervention group vs. 166 hours in the control group) and mortality. A patient's APACHE III score made no difference in the outcomes; neither did resident experience and training.

In a subanalysis, the authors determined that ratios were unchanged for patients admitted at night.

Having so many patients admitted at night was a strength of the study, the authors said. "If nighttime intensivists were effective, it is likely they would be particularly effective in an ICU with such a large nighttime workload," they wrote.

The researchers noted that further research is important because currently one-third of U.S. academic medical centers employ nighttime intensivists. On the surface, nighttime ICU staffing seems compelling, said the authors. But it also may be "one of several expensive medical practices that have been adopted without a supportive evidence base."

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VIEW ON THE NEWS

Dr. Steven Q. Simpson, FCCP, comments: This is a timely article, as medical centers of all types are grappling with the notion that in-house intensivists may improve quality, yet are very expensive. I agree with the authors that it is fortuitous that the majority of admissions occur at night and that the results are unlikely to be generalizable.

The authors omit two potential additional explanations for the negative result: 1) that a teaching service impairs care and interferes with the smooth running of processes during its half of the day in a way that cannot be overcome by a sole intensivist at night, and 2) that a daytime staff intensivist functioning all night one night a week is subject to fatigue, just like anyone who attempts to function without rest. It may be that the findings would be different if a full-time nocturnal intensivist were used.

The authors are to be lauded for giving some data on this subject where there has been little to none, and where extremely expensive actions have been taken with no proof that they would have any effect.

Study: Euglycemic insulin resistance may predict VAP

BY M. ALEXANDER OTTO
IMNG Medical News

LAS VEGAS – The development of euglycemic insulin resistance soon after intubation may herald the onset of ventilator-associated pneumonia, a study by Vanderbilt University investigators suggests.

Researchers compared 92 critically injured trauma patients who developed VAP (ventilator-associated pneumonia) 3-4 days after intubation with 2,162 who did not. All the subjects had their blood glucose levels kept mostly between 80 and 150 mg/dL with the help of a computer-assisted protocol that adjusted insulin drip rates as necessary, lead investigator Dr. Kaushik Mukherjee told the annual meeting of the Surgical Infection Society.

There were no differences in baseline demographics between the groups, but compared with controls, patients who developed VAP needed significantly higher insulin drip rates to stay in that range the day before and the first and third days VAP diagnosis (max. diff., 1.1 U/hr [95% CI, 0.8-1.5]).

The M multiplier, a surrogate for insulin resistance calculated from blood glucose levels and insulin drip rates, was significantly higher 2 days before VAP was diagnosed, and remained so for 10 days afterward.

If the findings are replicated, the Vanderbilt team says they may help predict who's at risk for VAP so that preventative measures can be taken. Among other things, the model will need to incorporate body mass index, steroid use, tube-feeding schedule, and other confounders that impact insulin requirements, and will need to be put through a prospective trial. Even so, "these data indicate euglycemic insulin resistance may be an important new indicator for VAP in the era of strict glycemic control. [This] may be valuable moving forward," said Dr. Mukherjee of Vanderbilt's trauma and surgical critical care division.

Patients in the study were at least 16 years old, and had been ventilated for at least 48 hours. Both VAP and control patients needed increasing amounts of insulin in the 10 days following intubation, probably "due to added nutrition, but [the VAP group required] a more rapid increase in their insulin infusion rates" starting about 3 days before diagnosis.

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CRITICAL CARE COMMENTARY: The Kansas Sepsis Project

BY DR. STEVEN Q. SIMPSON, FCCP

We established the Kansas Sepsis Project in 2009 to reduce the risk of mortality from severe sepsis by 10% by the end of 2015 in the state of Kansas. The long-term intent is to reduce mortality even further in this state and to extend our methods to be usable by anyone. Severe sepsis, by one name or another, is one of the oldest and most vexing human health problems. In 1513, Machiavelli wrote in *The Prince*, "as the physicians say it happens in hectic fever, that in the beginning of the malady it is easy to cure but difficult to detect, but in the course of time, not having been either detected or treated in the beginning, it becomes easy to detect but difficult to cure." Five hundred years later, severe sepsis remains underrecognized and undertreated in its earlier stages, resulting in mortality rates of 30% to 50%, and even higher if septic shock is not treated in an aggressive and timely fashion. In 1995, there were over 750,000 cases of severe sepsis in the United States, resulting in 500 deaths per day on average (Angus et al. *Crit Care Med*. 2001;29[7]:1303). The most recent epidemiological evidence indicates that there may now be as many as 3 million cases per year in the United States (Gaieski et al. *Crit Care Med*. 2013; 41[5]:1167).


DR. SIMPSON

Based on national data, it is estimated that 15,000 to 20,000 Kansans are afflicted with severe sepsis every year, and approximately 15 people die of severe sepsis on an average day in our state. Kansas is a largely rural state, but our population distribution is comparable to that of a large swath of states across the Great Plains and Mountain West. Nearly half of the state's inhabitants (48%) live in rural areas, and numerous counties have a population density < 6 persons per square mile, referred to as "frontier." At 82,276 square miles, Kansas is the 15th-largest state in geographic area, but its 2.85 million inhabitants place it as the 34th largest in population and 40th in population density. As a result, many of the state's inhabitants suffer from geographic health-care disparity. In truth, most rural inhabitants of the United States suffer geographic disparity in health care. One in four Americans lives in a rural area, yet only one in 10 physicians practices in a rural area.

The incidence of severe sepsis rises rapidly in people over the age of 65 years, increasing fivefold between the ages of 65 and 80. Since April 2011, more than 10,000 baby boomers each day have turned 65 and as many will continue do so for a total of 19 years, so severe sepsis will be a dominant force in medicine for a very long time. Physicians and other practitioners, regardless of their specialty, will be faced with patients with sepsis. However, over a decade after the consensus adoption of criteria for the diagnosis of severe sepsis, the majority of physicians were not well versed in recognizing severe sepsis (Poeze et al. *Crit Care*. 2004;8[6]:R409). This likely still holds true, especially for nonintensivist physicians.

Although the term *sepsis* was apparently first used by Hippocrates (sepsis is a form of the Greek word for putrefaction) an internationally accepted clinical definition of the syndrome was not published until 1992, based on the definitions first developed by Dr. Roger Bone at the University of Kansas in the late 1970s (Bone et al. *Chest*. 1992;101[6]:1644). Until that time, many definitions of the syndrome were applied with resultant disparity in the outcomes of clinical trials. Physicians and others who were trained prior to 1992, many of whom are now at the zeniths of their careers, were not exposed to this definition during their formative training.

To find out whether there is an existing gap in physician education and knowledge regarding severe sepsis in rural Kansas, we led a series of focus groups in 2007-2008 in six medium-sized towns in all geographic areas of the state. While the majority of providers considered themselves knowledgeable or very knowledgeable about sepsis, only a small minority were actually familiar with well-accepted evidence-based measures for the care of patients with severe sepsis, including early goal-directed therapy (EGDT), or the differentiation of patients with sepsis from those with severe sepsis or septic shock. One-third expressed the view that the problem with diagnosing severe sepsis is the lack of established diagnostic criteria. In the end, 80% of practitioners believed that further education in recognizing and treating severe sepsis would be "extremely" beneficial.

Based on this needs assessment and with financial support from The CHEST Foundation, we established the Kansas Sepsis Project. We previously had success in achieving a > 50% reduction in mortality at the University of Kansas Hospital and desired to help spread this success to other hospitals across the state. Of Kansas' 126 hospitals, 83 are critical access hospitals, for whom the challenges are of a different nature than those of our tertiary academic center. Critical access hospitals have 25 beds or fewer and are located at least 35 miles from the next hospital. By definition, these 83 hospitals are rural. Of the remaining hospitals, only 22 have over 100 beds, and only 12 are located in locations that qualify as urban.

We recruit hospitals of various sizes across the state to participate in a program of quality improvement in severe sepsis, for which physicians and nurses can receive continuing education credit, required for both medical and nursing licensure in all 50 states. The most effective continuing education is problem based, and we believe that the problem of improving care for severe sepsis cases is an ideal venue for problem-based learning that actually improves patient outcome. We developed and provided an online means of measuring and storing data regarding diagnosis and key treatment parameters for severe sepsis and of running serial reports to track performance over time and benchmark against other hospitals. For critical access hospitals, we developed an abbreviated version of EGDT that calls for antibiotics, fluids, vasopressors, and a triage decision within 2 hours for transport to a larger, supporting hospital.

As with many quality improvement initiatives, uptake over time has been mixed. In fact, some hospitals and physicians have declined to participate, even when shown the outstanding results of others just like them. At this writing, the project has earned acclaim and numerous hospitals as well as a large number of physicians in our state, are initiating their quality improvement efforts. Among successful enrollees, compliance with aspects of the sepsis bundles has increased by as much as 90% (absolute increase) and recognition of severe sepsis on presentation is also above 90%.

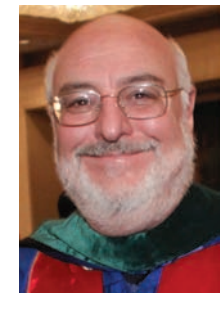
A truly important feature to residents of small towns is the ability to be treated "at home" in their own hometown hospital. On average, before participation in the Kansas Sepsis Project, 25% of rural patients with sepsis required transfer to a higher level of care; after initiation of quality improvement efforts, only 5% require that transfer. This is both comforting for rural residents and lifesaving for a 25-bed hospital straining to keep its doors open so that it can serve its community.

More information is available at the Midwest Critical Care Collaborative (mwcritcare.org) or the Kansas Sepsis Project (kansassepsisproject.org).

Dr. Simpson is professor of medicine, associate division director, and director of fellowship training, Division of Pulmonary and Critical Care Medicine, University of Kansas, Kansas City.

EDITOR'S COMMENTS

This commentary by Dr. Simpson is not only quite revealing but instructive. As we became more aware of sepsis and the need for early goal-directed therapy to improve outcomes, the recognition of the entity of sepsis has been lacking. Since 2005, it was estimated that there were 750,000 cases per year, and we now believe there are easily 3 million in the United States alone.



There is a shortage of both ICU beds and providers in the United States, and this will continue to escalate as the years progress. The Kansas Sepsis Project and its innovative collaborative style is a great example of what could be done and what needs to be done. Since not all states are the same, and not all medical systems are equally equipped, the need for this type of project is clear. As our population ages and recognition of sepsis hopefully continues to rise, resources will be better used and more lives will be saved.

Dr. Peter Spiro, FCCP
Section Editor
Critical Care Commentary

Beyond Our Walls: Advancing the Future of Chest Medicine

Support the campaign and cement your place in ACCP history.

BY MARILYN A. LEDERER, CPA

In 2014, the ACCP will move into a dynamic new headquarters in Glenview, Illinois, moving the College to a new model of educational delivery that is hands-on, in-depth, and flexible. With a year-round center for immersive training and innovation, as well as on-demand access to tools for physicians, the ACCP will have a platform to advance chest medicine and improve patient care.

The College's 48,500-SF, Silver LEED-certified headquarters will be housed on ample, verdant grounds that create a sense of calm retreat; facilitate exchange and collaboration; and, most importantly, reflect the College's commitment to environmental sustainability—and the cleaner air and healthier lungs it leads to. A cornerstone of the new learning campus is the 15,000-SF Innovation and Simulation Center.

Through a comprehensive curriculum offered at the Innovation and Simulation Center, the ACCP plans to address the full range of procedures members need to master in order to help every patient they treat. With a full-fledged educational experience that mixes lectures with small group activities and hands-on simulation, the College can help physicians adapt to the rapidly changing healthcare landscape and improve the lives of patients around the globe.

With the philanthropic investment of ACCP members, friends, and supporters, the ACCP can take the next great leap in advancing chest medicine with effects that will be felt well beyond its walls. The CHEST Foundation embarked on its *Beyond Our Walls: Advancing the Future of Chest Medicine* capital campaign at CHEST 2012. With a goal of $5 million, derived through the generosity of corporate supporters, ACCP members, and committed individuals, the ACCP will realize its vision. To date, the campaign has secured almost 50% of its campaign goal to be achieved by year-end 2013.

There are two important ways to support the new ACCP learning campus. Donations can be made through the following programs:

The new ACCP headquarters will be a year-round center for training and innovation.

Secure a customizable brick: With a gift of $1,000, you can buy a brick and cement your place in ACCP history. Each donor will be able to customize a concrete paver near the main entrance to the new headquarters building. Donors can pay tribute to a lifetime of work, memorialize a loved one, honor a friend or family member, or lend support to the fight for better respiratory health. There is a limited quantity of pavers available.

To reserve your paver, go to beyondourwalls.chestnet.org or contact Marilyn Lederer at mlederer@chestnet.org.

Make a gift: There are many opportunities to support the new ACCP learning campus. From buying a brick to donating a major gift to name spaces in the new facility, all levels of donations are appreciated. Learn more about how you can help by going to beyondourwalls.chestnet.org, where you take a virtual tour of the new building, learn about the capital campaign, and review the benefits of giving to this worthy endeavor.

To discuss a campaign gift, contact Marilyn Lederer at (847) 498-8370 or mlederer@chestnet.org.

The ACCP and The CHEST Foundation have always depended on philanthropic partners to improve patient care through education. Together, we can continue to make a difference.

NETWORKS: Omega-3s; reflux, plus; OLDs and OSA

Cardiovascular Medicine and Surgery

Omega-3 fatty acids

Omega-3 fatty acids (n-3 fatty acids) are commonly used to reduce triglyceride levels.[1] Their place in therapy for treating cardiovascular disease has been established by notable landmark studies such as GISSI-Prevenzione trial, GISSI Heart Failure study, and the Japan EPA Lipid Investigation Study (JELIS).[2-4]

In a recent randomized, placebo-controlled study published in the *New England Journal of Medicine*,[5] n-3 fatty acids did not reduce the revised primary endpoint of time to death from cardiovascular (CV) causes or hospital admission for CV causes. Unlike previous trials that studied patients with a history of myocardial infarction[2, 4] and heart failure,[3] this study was conducted in a primary prevention population of patients with multiple risk factors for CV disease or clinical evidence of atherosclerotic vascular disease.

Over 12,000 patients in Italy were randomized to receive either 1 g of n-3 fatty acids or placebo (olive oil). After 5 years of follow-up, the primary endpoint occurred in 733 of 6,239 (11.7%) patients who received n-3 fatty acids compared with 745 of 6,266 (11.9%) patients in the placebo group (adjusted HR 0.97; 95% CI 0.88 to 1.08; $P = .58$). Additionally, the two groups did not differ significantly in the study's secondary endpoints, such as sudden death from cardiac causes and death from CV causes. Rates of adverse events were similar between the two groups. It must be noted that the investigators had to change their primary endpoint 1 year into the study due to a lower than expected event rate. The primary efficacy endpoint as defined in the beginning of the trial was the cumulative rate of death, nonfatal MI, and nonfatal stroke. The endpoint was then changed to the composite of time to death from CV causes or hospital admissions for CV causes. The applicability of this study to the American population is debatable since this was conducted exclusively in the Italian population. It is possible that the study population already had a diet reflective of the "Mediterranean diet," which is higher in polyunsaturated fatty acids, fruits, vegetables, nuts, and seeds and lower in saturated fat and red meat compared with the typical American diet.

Dr. Jun R. Chiong, FCCP
Ex Officio NetWork Member

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Chest Infections

Aerodigestive chest infections in the elderly: when reflux is more than reflux

Mrs. Smith is a delightful and spunky 78-year-old woman who lives in Palm Springs, California, enjoys playing

Continued on following page

Continued from previous page

bridge, and watches reruns of *Matlock*. She has a chronic cough that alienates her from her friends. She has no gag reflex, speaks with a gurgling voice, and coughs when drinking. She was admitted four times last year for pneumonia.

Many elderly patients have aspirations that land them in the hospital with pneumonia. They carry the diagnosis of reflux, but their studies show "little aspiration," underestimating their problem. Impaired secretion clearance, medication-related diminished production of saliva, dental disease due to poor oral hygiene, chronic pharmacologic acid suppression, late dinners, and sleep aids that change their sleep architecture are all factors that make cough due to oropharyngeal dysfunction in elderly patients quite frequent.

Such disorders can constitute a threat for life due to malnutrition, dehydration, hypoxia, respiratory failure, and cardiac arrest. The health-care provider is challenged by the desire to alleviate a symptom that alters quality of life while not subjecting the patient to invasive diagnostics.

Effective management requires a multidisciplinary aerodigestive team approach. This includes a careful assessment of the oropharyngeal anatomy; nutritional status; cognition; swallowing retraining; lifestyle modifications (eg, elevation of the head of bed); separation of phonation and deglutition; eating small, thickened meals several times a day; and aggressive oral care. It may be time for aerodigestive centers akin to the ones already in place for children.

Dr. Hassan Bencheqroun, FCCP
Steering Committee Member

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Clinical Pulmonary Medicine

On obstructive lung disease and obstructive sleep apnea: time to revisit nosologies?

Obstructive lung diseases (OLDs), such as asthma, chronic bronchitis, emphysema, or COPD are very prevalent conditions. OLD definitions: (1) span distinct domains (clinical, functional, anatomical, tomographic, etc); (2) frequently overlap; and (3) are defined functionally by either pre- or postbronchodilator FEV_1/FVC ratio (R). Fixed (0.70) vs lower-limit-of-normal R thresholds could either underestimate or overestimate OLD prevalence; similarly, postbronchodilator (vs prebronchodilator) R may also underestimate the prevalence of COPD, especially in younger subjects.

Several recent and promising attempts have been proposed to explore OLD phenotypes with newer methodologies (eg, cluster analysis, genomics, metabolomics, proteomics, etc), which do not rely on a priori assumptions on best-split levels for different OLD categories.

Obstructive sleep apnea (OSA) is also a common condition that features bidirectional interactions with OLDs. They share a number of risk factors, such as obesity, smoking, nasal disease, increased airway resistance, and local and systemic inflammation. OSA is associated with worse clinical outcomes in patients with OLD, while positive airway pressure therapy seems to have beneficial effects in this setting.

While the term *overlap syndrome* has been used before for the comorbid association of COPD and OSA, we recently proposed the term *alternative overlap syndrome* for asthma and OSA.

In an effort to further encourage investigations in this area, we also proposed an integrated, lumping nomenclature for OSA in the setting of OLD, OLDOSA (obstructive lung disease and obstructive sleep apnea) syndrome.[1]

In the future, this relumping approach will hopefully become productive by generating more refined and robust phenotypic or nosologic characterizations.

Dr. Octavian C. Ioachimescu, PhD, FCCP
Vice-Chair

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Ultrasound: The bread and butter of intensivists

BY DR. SETH KOENIG, FCCP
Section Editor, Ultrasound Corner, CHEST

Ultrasound use in ICUs is gaining momentum as more critical care physicians realize the effectiveness of point-of-care, goal-directed ultrasounds in the management of their patients, both for procedural guidance and as diagnostic tools.

Through well-designed studies and numerous critical care ultrasound hands-on courses offered through the ACCP and others, the opportunities to acquire the cognitive aspect of ultrasound, image acquisition, and interpretation skills continue to grow.

To this end, *CHEST* has launched a new video-based ultrasound case-based series called Ultrasound Corner. Its focus is to bridge image acquisition, interpretation skills, and its application to the critically ill patient. While the intensivist may gain proficiency in ultrasound image acquisition and interpretation with relative ease, its application to a critically ill patient may be more challenging.

This video-based ultrasound case format may fill a need for our readers by combining the clinical case scenario and physical exam with an appropriate logical, goal-directed ultrasound exam. Case patient video images will be compared with normal patient video images, allowing the intensivist immediate distinction. Videos will be accompanied by both labeled still images and voice narration to further illustrate the main teaching point of each case.

While rare and fascinating case reports interest both readers and editors for publication, Ultrasound Corner will focus on common, everyday clinical situations and the application of goal-directed ultrasound for diagnosis and management.

The rapid assessment of patients presenting with cardiopulmonary failure is the bread and butter of all intensivists; these cases are intended to provide guidance with ultrasonography to categorize shock states (cardiogenic, distributive, obstructive, etc) and to search for an etiology of respiratory failure using thoracic ultrasound. Interested members may also take an active role in this new series by submitting their video-based ultrasound cases for publication in *CHEST* (http://journal.publications.chestnet.org/ss/forauthors.aspx).

Community and Engagement Work Group makes debut

The ACCP has recognized changing environmental trends in regard to associations and membership organizations as shifting demographics are impacting the marketplace. In an effort to ensure ACCP's leadership position and relevancy in this changing environment, the Community and Engagement Work Group will explore new strategies to assist the ACCP in taking advantage of these new opportunities.

The Community and Engagement Work Group will facilitate research leading to the recommendation of potential new strategies for fostering community and increasing engagement in the ACCP that will create an environment of participation on a global scale.

The Work Group had their first meeting on May 13 and will continue meeting throughout 2013. The group will present a high-level, strategic proposal to the Board of Regents in March 2014 to coincide with ACCP's overall strategic planning.

This Month in *CHEST*: Editor's Picks

BY DR. RICHARD S. IRWIN, MASTER FCCP

CHEST Editor in Chief

Whole Blood Lactate Kinetics in Patients Undergoing Quantitative Resuscitation for Severe Sepsis and Septic Shock. *By Dr. M. A. Puskarich et al.*

Excessive Daytime Sleepiness and Obstructive Sleep Apnea in Patients With Sarcoidosis. *By Dr. K. C. Patterson et al.*

A Placebo-Controlled, Randomized Trial of Mesenchymal Stem Cells in COPD. *By Dr. D. J. Weiss et al.*

A Proposal for Combination of Total Number and Anatomical Location of Involved Lymph Nodes for Nodal Classification in Non–Small Cell Lung Cancer. *By Dr. H. Saji et al.*

Flock Worker's Lung Disease: Natural History of Cases and Exposed Workers in Kingston, Ontario. *By Dr. S. E. Turcotte et al.*

PULMONARY PERSPECTIVES: Preoperative functional evaluation of lung resection candidates

BY DR. ALESSANDRO BRUNELLI, FCCP

The American College of Chest Physicians has recently published the third edition of the evidence-based clinical practice guidelines on lung cancer management (Diagnosis and Management of Lung Cancer, 3rd ed. ACCP Evidence-Based Clinical Practice Guidelines. *Chest.* 2013;143[5]:e1S-e512s). The physiology chapter summarizes the most recent evidences regarding functional evaluation of the lung resection candidates, which are synthesized in a functional algorithm (Fig 1). There are important differences compared with the second edition.

The panelists emphasized the importance of a preliminary cardiologic evaluation and proposed a simple flow chart centered on the use of a scoring system to stratify the cardiac risk. The Thoracic Revised Cardiac Risk Index (ThRCRI) is a refinement of the original RCRI (Lee et al. *Circulation.*1999;100[10]:1043), which was recalibrated and subsequently validated in specific thoracic surgery patient settings (Brunelli et al. *Ann Thorac Surg.* 2010;90[1]:199; Ferguson et al. *Eur J Cardiothorac Surg.* 2012; 41[3]:598). The ThRCRI is composed by four weighted factors: creatinine >2 mg/dL= 1 point; pneumonectomy = 1.5 points; previous stroke or transient ischemic attack (TIA) = 1.5 point; previous ischemic heart disease = 1.5 points. A score greater than 1.5 corresponds to a risk of major cardiac events up to 10% to 20% (Brunelli et al. *Ann Thorac Surg.* 2010;90[1]:199; Ferguson et al. *Eur J Cardiothorac Surg.* 2012;41[3]:598).

Patients with a ThRCRI >1.5, with a known underlying cardiac disease, or with significant exercise limitations need to be seen by a cardiologist and managed according to the American Heart Association/American College of Cardiology guidelines (Fleisher et al. *Circulation.* 2007; 116[17]:e419). All the others can be fast tracked to pulmonary function tests.

The panelists confirmed the recommendation to systematically measure FEV_1 and DLCO in all candidates to lung resection based on the fact that these two parameters are only moderately correlated and are the expression of two different aspects of the pulmonary function. At variance with previous guidelines, only the predicted postoperative values of FEV_1 and DLCO (ppoFEV_1 and ppoDLCO) and expressed percentage of predicted values are taken into consideration for risk stratification (but not their preoperative values). This represents a great simplification of the algorithm compared with previous versions. Patients with either ppoFEV_1 or ppoDLCO >60% and with negative or positive low-risk cardiologic evaluation are classified at low risk for pulmonary anatomic resections, and no further tests are recommended.

Patients with either ppoFEV_1or ppoDLCO <60%, but both values >30%, need to be evaluated further with an exercise test. This step has two caveats: the cutoff value of 60% for PPO values was derived from expert opinion and indirect evidence (limited specific evidence exists in the literature); and cardiopulmonary exercise tests (CPET) should ideally be performed in these patients. However, if CPET is not readily available, low-technology tests, such as a stair-climbing test or a shuttle-walking test, are sufficient to screen this group of patients.

Those patients showing a satisfactory performance at low-technology exercise test (eg, >22 m of height at stair-climbing test or >400 m at shuttle-walking test) are classified at low risk for pulmonary anatomic resections.

On the contrary, those with a poorer performance at stair-climbing test or shuttle- walking test need to be referred for a formal CPET. This latter test is recommended also for those patients with a positive high-risk cardiac evaluation regardless pulmonary function and for those patients with either ppoFEV_1 or ppoDLCO <30% predicted.

Although maximum oxygen consumption (VO_2max) is the measure most frequently used for risk stratification, CPET yields a series of other direct and indirect measures, which can help in identifying the possible deficits in the oxygen transport system, distinguishing between cardiovascular, pulmonary vascular, respiratory causes of a reduced aerobic capacity.

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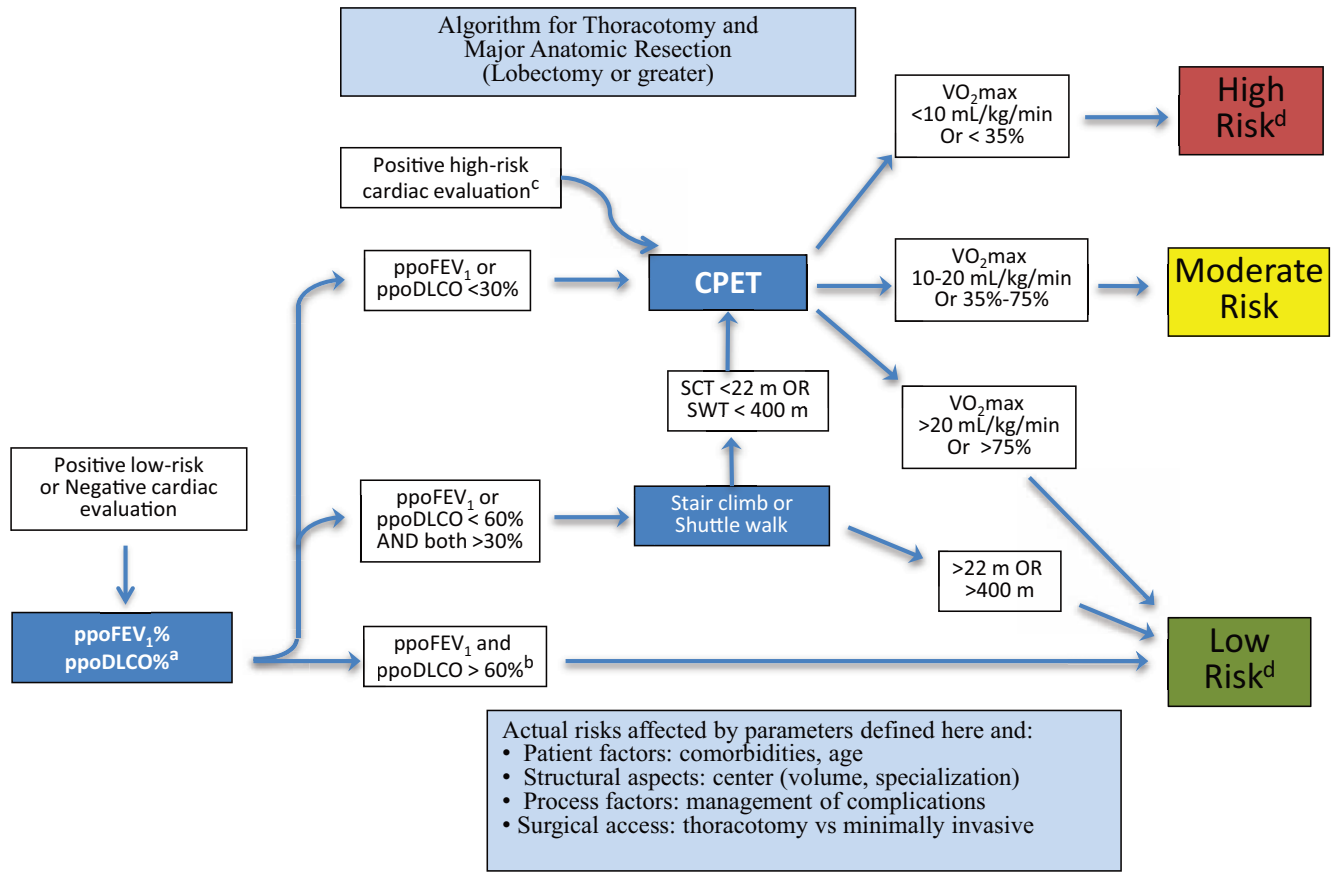

Algorithm for thoracotomy and major anatomic resection (lobectomy or greater). For a = for pneumonectomy candidates, we suggest to use Q scan to calculate predicted postoperative values of FEV_1 or DLCO (PPO values = preoperative values × (1 - fraction of total perfusion for the resected lung), where the preoperative values are taken as the best measured postbronchodilator values. For lobectomy patients, segmental counting is indicated to calculate predicted postoperative values of FEV_1 or DLCO (PPO values = preoperative values × (1 - y/z), where the preoperative values are taken as the best measured postbronchodilator value and the number of functional or unobstructed lung segments to be removed is y and the total number of functional segments is z; b = ppoFEV_1 or ppoDLCO cutoff values of 60% predicted values have been chosen based on indirect evidences and expert consensus opinion; c = for patients with a positive high-risk cardiac evaluation deemed to be stable to proceed to surgery, we suggest performing both pulmonary function tests and cardiopulmonary exercise test for a more precise definition of risk; and d = definition of risk:

Low risk = expected risk of mortality is below 1%. Major anatomic resections can be safely performed in this group; moderate risk = morbidity and mortality rates may vary according to the values of split lung functions, exercise tolerance, and extent of resection. Risks and benefits of the operation should be thoroughly discussed with the patient; and high risk = the risk of mortality after standard major anatomic resections may be greater than 10%. Considerable risk of severe cardiopulmonary morbidity and residual functional loss is expected. Patients should be counseled about alternative surgical (minor resections or minimally invasive surgery) or nonsurgical options.

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In addition, several studies have shown that CPET is a useful tool to detect both symptomatic or asymptomatic exercise-induced myocardial ischemia with a diagnostic accuracy similar to myocardial perfusion study and superior to ECG stress testing, providing several variables,eg, oxygen consumption relative to heart rate and work rate, showing consistent, quantitative patterns of left ventricular dysfunction caused by myocardial ischemia.

'Most importantly, and at variance with previous versions, the current guidelines attempt to define the concept of surgical risk.'

A $V_O_2$max >20 mL/kg/min or >75% predicted is associated with a low risk for major anatomic pulmonary resections. A value of $V_O_2$max <10 mL/kg/min or <35% predicted is associated with a high risk for major anatomic pulmonary resections. Values of $V_O_2$max between 10 and 20 mL/kg/min (or between 35% and 75% predicted) are associated with a moderate risk.

The use of CPET for preoperative evaluation is subject to two important caveats.

First, in order to ensure reliability of results, the test must be performed according to the recommendations published by the American Thoracic Society/American College of Chest Physicians statement on cardiopulmonary exercise testing (Brooks et al. *Am J Crit Care Respir Med*. 2003;167[9]:1287).

Second, some candidates for lung resection are unable to perform some or all types of exercise tests for incapacitating comorbidities. These patients should be regarded as high-risk patients, and they should be carefully evaluated based on the available cardiac and pulmonary parameters.

In addition to the parameters included in the algorithm (cardiac and pulmonary function and exercise capacity), the panelists acknowledged that the surgical risk may depend upon other factors, such as age, comorbidities, structural characteristics of the thoracic surgery unit (eg, volume and specialization), pathways of care (eg, management of complications), and surgical approach (thoracotomy or minimally invasive).

Most importantly, and at variance with previous versions, the current guidelines attempt to define the concept of surgical risk.

Low risk is defined as an expected risk of mortality below 1%. Major anatomic resections can be safely performed in this group.

Moderate risk is defined as a risk of morbidity and mortality, which can vary according to the values of split lung functions, exercise tolerance, and extent of resection. Risks and benefits of the operation should be thoroughly discussed with the patient.

High risk is defined as a risk of mortality greater than 10% after standard major anatomic resections. Considerable risk of severe cardiopulmonary morbidity and residual functional loss is expected. Patients should be counseled about alternative surgical (minor resections or minimally invasive surgery) or nonsurgical options whenever feasible.

One important limitation of currently available evidence on preoperative functional evaluation is the paucity of information about patient perspectives and expectations. Objective factors commonly used to predict traditional outcomes, such as morbidity and mortality, have been shown to be poorly associated with the perceived residual quality of life. Patient expectations and concerns about their residual quality of life are important factors that play an important role in the decision to proceed to surgery. In this regard, future research will be needed to refine current functional guidelines by including specific factors associated with residual quality of life.

Dr. Brunelli is Chief, Section of Minimally Invasive Thoracic Surgery, and Vice-Director of the Division of Thoracic Surgery, Ospedali Riuniti, Ancona, Italy; and the Secretary General of the European Society of Thoracic Surgeons.

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