



AMERICAN COLLEGE OF SURGEONS

SURGERY NEWS

New Guidelines Suggest Changes in Sepsis Management

BY MITCHEL L. ZOLER
Elsevier Global Medical News

The revised guidelines for managing severe sepsis and septic shock published by the Surviving Sepsis Campaign early this year updated and changed the group's 2004 guidelines, and introduced a new system for assessing the evidence behind the guidelines.

Two notable changes contained in the revised guidelines were lowering to a "weak recommendation" the grade for using intravenous hydrocortisone to treat adults with septic shock who are poorly responsive to fluid resuscitation and vasopressor therapy, and lowering to a "weak recommendation" the grade for treating adult patients with sepsis-induced organ dysfunction and an Acute Physiology and Chronic Health Evaluation (APACHE) II score of 25 or greater with recombinant human activated protein C (rhAPC) (*Crit. Care Med.* 2008;36:296-327).

These two revisions were the major changes, said Dr. Jeffery S. Vender, who represented the American College of Chest Physicians on the guidelines writing committee, and is professor of anesthesiology and critical care medicine at Northwestern University, Chicago.

In both cases, these downgrades occurred because data from recent trials raised questions about efficacy and also suggested a risk of hemorrhage when treating patients with rhAPC. Steroid use became a weak recommendation "in light of conflicting trial results," and use of rhAPC became a weak recommendation

to bring its use "in line with current labeling from European and U.S. regulatory agencies," said Dr. R. Phillip Dellinger, chairman of the guidelines writing committee.

Other changes included strong recommendations for achieving a central venous oxygen saturation of 70% or greater, achieving glycemic control, using head-of-bed elevation for mechanically ventilated patients, placing a 6-hour target for verifying the source of infection, and allowing tidal volumes higher than 6 mL/kg of predicted body weight in ventilated patients when clinical problems arise from the 6 mL/kg target, added Dr. Dellinger, head of the division of critical care medicine at Cooper University Hospital in Camden, N.J.

Emergency physicians need to be careful about timing a patient's APACHE II score when deciding whether to treat with rhAPC, warned Dr. Emanuel Rivers.

Severe sepsis patients can have scores higher than 30 initially that then fall below 25 after aggressive, initial therapy, said Dr. Rivers of the department of emergency medicine and critical care at Henry Ford Hospital in Detroit. He recommended that physicians first treat patients following the new guidelines for 6-12 hours, and then measure the APACHE II score to determine whether treatment with rhAPC is indicated.

Another substantial change in the revised recommendations is the implementation of a new system for grading and classifying the evidence that supports the guidelines.

"We recognized that criticism about the grading system used for the prior guidelines pointed to valid limitations," Dr. Dellinger said in an interview. "We were able to partner with the world's leading evidence-based medicine group, the GRADE Working Group, for the revision, and our

A NEW SYSTEM FOR GRADING AND CLASSIFYING THE EVIDENCE THAT SUPPORTS THE GUIDELINES HAS BEEN IMPLEMENTED TO ADDRESS PRIOR LIMITATIONS.

new system is much better."

"We're generally happy with the scientific merit of the guidelines," commented Dr. David H. Ingbar, president of the American Thoracic Society.

Reviewers performed a scientific assessment of the guidelines on behalf of the ATS, and most of their initial concerns were resolved, added Dr. Ingbar, professor of medicine and director of the pulmonary, allergy, critical care, and sleep division of the University of Minnesota, Minneapolis.

The only unresolved ATS concerns focused on the strength of certain recommendations rather than the recommendations themselves. The ATS reviewers also raised conflict-of-interest concerns about the guidelines that ultimately led the ATS to withhold its endorsement.

"It's good that the guidelines made

rhAPC a weak recommendation," commented Dr. Peter Q. Eichacker, head of the critical care section and senior investigator at the National Institutes of Health in Bethesda, Md. "Clearly there is an increased risk of bleeding in patients treated with rhAPC, especially when the drug is used outside of the very controlled setting of a clinical trial."

Dr. Eichacker also highlighted the uncertainty surrounding the recommendation to use central venous oxygen saturation to guide therapy, pointing out that the benefits of this approach were documented by one study done at a single medical center.

Other concerns about the revised guidelines include the recommendation of intravenous insulin to reduce blood glucose levels, because "the incidence of hypoglycemia is substantial" in patients with septic shock, Dr. Eichacker said in an interview.

Furthermore, he noted that there is controversy on how low the tidal volume should be for patients with severe sepsis who are on mechanical ventilation.

"The Institute for Healthcare Improvement says that the components of a treatment bundle [the format used in the sepsis guidelines] should have irrefutable evidence for their use. Treatments such as steroids, rhAPC, and intensive insulin therapy are not backed with irrefutable evidence," Dr. Eichacker said. They are still undergoing study in trials, yet they have been incorporated in the bundles—a shortcoming of the new guidelines, he added. ■

Obesity Tied to Respiratory Problems in Pediatric Surgery

BY ELIZABETH MEHCATIE
Elsevier Global Medical News

Difficult mask ventilation, airway obstruction, and other respiratory-related adverse events were significantly more common in obese children and adolescents undergoing surgery than in normal-weight children, according to a prospective study of more than 2,000 pediatric patients.

The study results "support our hypothesis that the incidence of perioperative adverse respiratory events is increased in children who are obese," study investigators reported in the March issue of *Anesthesiology*.

The authors conducted the study because of what they described as the "paucity" of information on outcomes in overweight or obese children who undergo anesthesia and surgery.

The nonrandomized, nonblinded study enrolled 1,380 normal-weight, 351 overweight, and 294 obese children aged 2-18 years undergoing noncardiac elective surgery over 18 months. Weight category was based on age- and gender-adjusted body mass index (BMI), wrote Alan R.

Tait, Ph.D., and his associates in the anesthesiology department at the University of Michigan, Ann Arbor.

For clarity of analysis and presentation, the researchers limited their analysis to only two groups: obese and nonobese (normal and overweight combined).

Obese children were significantly older than nonobese children (mean age 11 years vs. 9 years), and had a significantly higher prevalence of comorbidities, including asthma (28% vs. 17%), hypertension (2.4% vs. 1.1%), obstructive sleep apnea (14% vs. 7%), gastric reflux (16% vs. 9%), and type 2 diabetes (2.7% vs. 0.1%) (*Anesthesiology* 2008;108:375-80).

The investigators collected data on respiratory adverse events at five time points: at induction, during endotracheal intubation or placement of a laryngeal mask airway, during maintenance, at emergence, and during postoperative recovery.

In both groups, endotracheal intubation was successful on the first try in about 88%-90% of cases.

Most types of airway and respiratory adverse events, including critical events, were significantly more common in the obese children than in nonobese children. Difficult

mask ventilation was more than four times higher in the obese patients (9% vs. 2%), severe airway obstruction nearly twice as high (19% vs. 11%), bronchospasm three-fold higher (6% vs. 2%), and major oxygen desaturation almost twice as high (17% vs. 9%). Overall, adverse events were 24% higher and critical adverse respiratory events 60% higher in the obese group, compared with the nonobese group.

Factors that were significantly associated with critical respiratory events included asthma, obesity, snoring, a history of obstructive sleep apnea, age younger than 10 years, endotracheal intubation, and procedures involving the airway.

After discharge from the hospital, 5% of the obese children experienced nausea and vomiting at home, compared with 17% of the nonobese children.

Current trends indicate that anesthesiologists will continue to care for increasing numbers of overweight or obese children. Understanding the risk factors for perioperative adverse respiratory events will be important in anticipating and recognizing potential complications, and, in optimizing care, the investigators wrote. ■

FDA Panel Backs Limited Use of ESAs in Oncology

Panel favors informed consent to ensure patients' awareness of risks and benefits.

BY ELIZABETH MEHCATIE

Elsevier Global Medical News

GAITHERSBURG, MD. — A federal advisory panel voted 13-1 that erythropoietin-stimulating agents should continue to be marketed for chemotherapy-induced anemia despite concern that their use could have a negative impact on survival in cancer patients.

The panel, the Food and Drug Administration's Oncology Drugs Advisory Committee (ODAC), also voted 11-2, with one abstention, that these agents should not be indicated for patients whose cancers are considered curable. The panel met March 13.

In a closer 9-5 vote, the committee also recommended that these agents no longer be indicated for patients with metastatic breast and/or head and neck cancers, two tumor types in which a signal for increased mortality and tumor promotion has been duplicated. It voted 8-6, however, against restricting use of ESAs to patients with small cell lung cancer, a disease in which ESAs have not been shown to interfere with survival.

In an 8-5 vote with 1 abstention, the panel recommended that the FDA require informed consent for patients receiving treatment with ESAs for chemotherapy-induced anemia. This would require both patient

and physician signatures to ensure that physicians discuss the risks and benefits of ESA treatment as well as alternative treatments with patients. Most panel members, however, voted against mandating a restricted distribution system for ESAs when used to treat oncology patients.

The FDA held the meeting because two studies reported in January found an association between ESA use in cancer patients and increased mortality and/or tumor promotion. The black box warning for ESAs was updated on March 7 to include a statement about these findings.

There are now eight controlled clinical trials that provide evidence of increased mortality and/or tumor promotion in patients who receive ESAs and are being treated for head and neck cancer, breast cancer (in both neoadjuvant and metastatic settings), non-small cell lung cancer, or cervical cancer, as well as in cancer patients with anemia who are not receiving active anti-cancer treatment, according to the FDA. Only studies in patients with small cell lung cancer have "reasonably" excluded an increased mortality risk among patients receiving ESAs, the agency said, adding that other tumor types "have not been adequately studied."

The panel's votes sent a "clear signal" that this class of drugs should continue to be used to treat chemotherapy-induced ane-

mia but with label modifications, Dr. Richard Pazdur, director of the FDA's Office of Oncology Drug Products, said during a press briefing after the meeting concluded.

Dr. John Jenkins, director of the FDA's Office of New Drugs, added that it was clear the panel was concerned about the risks based on the available data, but more data are needed to clarify the risks further.

The FDA will have internal meetings about the panel's recommendations and meet with ESA manufacturers to discuss labeling changes but will probably issue interim recommendations for physicians before the final changes are made. The FDA usually follows the recommendations of its advisory panels, but recently overruled an ODAC recommendation against an indication for bevacizumab (Avastin) in metastatic breast cancer.

A statement issued by Amgen Inc. after the meeting said the company takes the safety signals in recent trials "very seriously," and would work with the FDA to consider the panel's recommendations. Amgen manufactures the three ESAs currently marketed in the United States, two epoetin alfa products (Procrit and Epogen) and darbepoetin alfa (Aranesp). Procrit is licensed to Johnson & Johnson.

Other approved indications for ESAs include the treatment of anemia associated with chronic renal failure; epoetin alfa has been approved for use with zidovudine therapy in patients with AIDS and for presurgical

administration to reduce perioperative transfusion requirements.

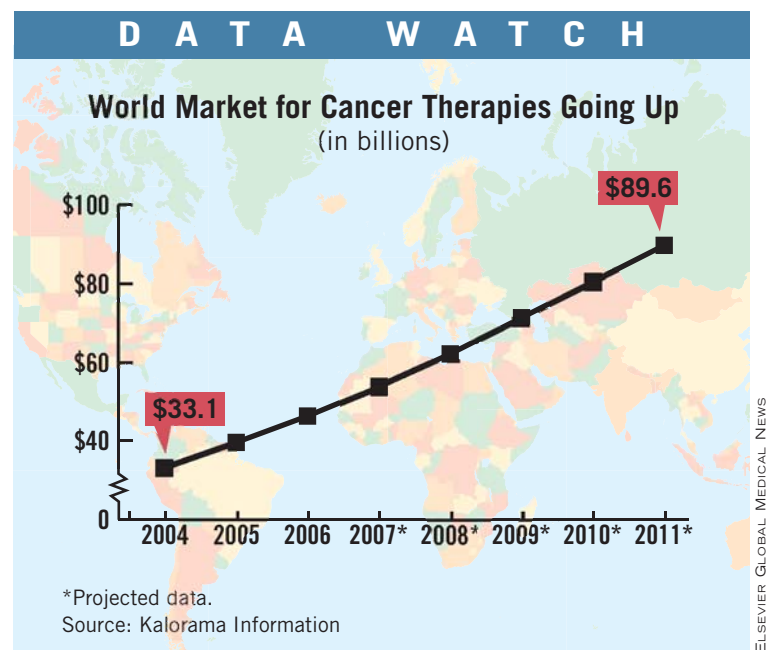
Amgen continues to study ESA risks in oncology patients. The company is conducting a pharmacovigilance study in patients with small cell lung cancer; it so far has found no difference in survival. A proposed Amgen study of more than 6,000 patients with advanced breast, lung, or colorectal cancer will compare overall survival and progression-free survival in patients who receive darbepoetin alfa (dosed to target a hemoglobin level of 12 g/dL) or placebo.

Dr. Wyndham Wilson, head of the lymphoma therapeutics section in the National Cancer Institute's Center for Cancer Research, Bethesda, Md., said that, for patients with potentially curable cancer, ESAs would be considered far riskier, "because you

may convert a curative patient to a noncurative patient."

One of the panelists, Dr. Judith Kramer of Duke University, Durham, N.C., voted against continued use of ESAs for treating chemotherapy-induced anemia because while an ESA is much more convenient than a red blood cell transfusion, the treatment could be accelerating mortality.

Another panelist, Dr. Michael Perry, who is director of the division of hematology/medical oncology at the University of Missouri-Columbia, said that while the viral risks of transfusions have decreased since ESAs first became available, blood transfusions are difficult and can be hazardous and that stopping the use of ESAs for anemia would likely result in a shortage of red blood cells. ■



Transplant Drugs Under Scrutiny For Safety Concerns

BY ELIZABETH MEHCATIE

Elsevier Global Medical News

The Food and Drug Administration is investigating a "potential association" between two drugs used to prevent organ rejection and the development of progressive multifocal leukoencephalopathy, a rare, often fatal progressive disorder that affects the central nervous system, the Food and Drug Administration announced on April 10.

The two drugs are mycophenolate mofetil (CellCept), manufactured by Roche, and mycophenolic acid (Myfortic), manufactured by Novartis Corp. CellCept is approved for preventing heart, liver, and kidney transplant rejection; Myfortic is approved for preventing kidney transplant rejection. (Mycophenolic acid is a metabolite of mycophenolate mofetil.) Both are approved for use with cyclosporine and corticosteroids.

In a notice posted on its MedWatch Web site, the FDA stated that Hoffmann-

La Roche Inc. has received postmarketing reports of progressive multifocal leukoencephalopathy (PML) in patients on CellCept and in patients on Myfortic, and has submitted an evaluation of the PML cases in the CellCept-treated patients. Roche

PATIENTS AND HEALTHCARE PROFESSIONALS SHOULD BE AWARE OF THE POSSIBILITY OF PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY.

also has submitted proposed changes to the prescribing information for CellCept. The data and the proposed changes are being reviewed by the FDA, which has requested that Novartis also submit data on PML cases in patients on Myfortic and to make similar changes to its prescribing information.

Roche is aware of PML cases in transplant recipients and in patients with systemic lupus erythematosus, according to the FDA statement. Neither drug is approved for treating SLE or similar autoimmune diseases.

The FDA expects the review to take about 2 months, after which the agency will make its conclusions and recommendations available to the public. "Until further information is available, patients and healthcare professionals should be aware of the possibility of PML, such as localized neurologic signs and symptoms in the setting of a suppressed immune system, including during therapy with CellCept and Myfortic," the notice said.

The FDA emphasized that the announcement does not indicate that the agency has concluded there is a causal relationship between the two drugs and PML or that health care professionals should stop prescribing the drugs.

PML, which usually affects patients who are immunosuppressed because of a dis-

ease or medications, occurs when the JC virus, a usually latent human polyomavirus, is activated. Once activated, the virus attacks cells that make myelin, resulting in symptoms that may include localized neurologic signs and possible vision changes, loss of coordination, clumsiness, memory loss, and leg weakness.

After several cases of PML were reported in patients who were treated with the immune modulator natalizumab (Tysabri) soon after it was approved for treating relapsing forms of multiple sclerosis in November 2004, it was taken off the market. But natalizumab was reintroduced in the United States in 2006, under a stringent risk-management program that restricts its distribution and use. ■

More information is available at www.fda.gov/medwatch/safety/2008/safety08.htm#mycophenolate. Adverse reactions associated with CellCept or Myfortic should be reported to the FDA's MedWatch program at 800-332-1088 or www.fda.gov/medwatch.