



Usefulness of Recombinant Human Erythropoietin in Critically Ill Patients

John Anderson, DO, & Maritza L. Groth, MD, FCCP

Abstracts From Literature

SYNOPSIS: *Weekly administration with 40,000 units of recombinant human erythropoietin decreases the number of allogeneic red blood cell transfusions in critically ill patients, without favorably affecting mortality.*

SOURCE: *Corwin H et al. Efficacy of recombinant human erythropoietin in critically ill patients. JAMA. 2002;288:2827-2835.*

The purpose of the present study was to evaluate the efficacy of weekly dosing of recombinant human erythropoietin (rHuEPO) in reducing red blood cell (RBC) transfusions in critically ill patients.

This was a prospective, randomized, double-blind, placebo-controlled, multicenter trial conducted between December 1998 and June 2001; 65 United States medical centers participated in the study. Patients were eligible if they were admitted to either a medical, surgical, or a medical/surgical intensive care unit (ICU) for at least 48 hours. Inclusion criteria were as follows: ICU stay of at least 3 days, age >18 years, hematocrit (Hct) < 38%, and ability to sign informed consent. Patients were ineligible if they had renal failure on dialysis, uncontrolled hypertension, new onset or uncontrolled seizures, acute burns, pregnancy or lactation, acute ischemic heart disease or acute gastrointestinal bleeding, or if they had received prior treatment with rHuEPO, had participated in another research protocol, or were expected to be discharged from the ICU within 48 hours.

Once enrolled into the study, patients received the study drug (40,000 units of rHuEPO) or a placebo by subcutaneous injection on

ICU day 3 and then weekly for those who remained in the hospital, for a total of 3 doses (study days 1, 7, and 14). If a patient remained in the ICU by study day 21, they received a fourth dose. The study drug was not administered on the scheduled day if the Hct was >38%. All patients were given oral elemental iron at a dose of at least 150 mg/d starting on study day 1, unless not tolerated. Parenteral iron was given to patients not responding to oral iron (transferrin saturation <20% and a decrease of serum ferritin to <100 ng/mL). Transfusions of pRBC were given at the discretion of the patient's physician. Guidelines for transfusion were proposed: no RBC transfusion if the hemoglobin (Hgb) level was >9 g/dL or the Hct was >27%, except in specific clinical situations such as active bleeding or ischemia. Transfusing at a hemoglobin <9 g/dL or a hematocrit <27% was at the discretion of the physician. All patients were followed to study day 28.

Baseline demographic, diagnostic, and laboratory data were obtained at the time of randomization. APACHE II scores were calculated based on data obtained in the first 24 hours after ICU admission, as well as admitting diagnosis and comorbidities. Initially, 33,685 pa-

tients were screened and 9674 fulfilled inclusion criteria, but 7055 were not approached for consent, and 1317 refused consent. As a result, 1302 were randomized, 652 assigned to placebo, and 650 to rHuEPO (study group). In the placebo group, 621 completed the study, but all 652 were included in the statistical analysis. In the study group, 614 completed the study and all 650 were included in the statistical analysis. From those in the study group 15% received one dose, 31% received two doses, 37% received three doses, and 17% received four doses of therapy.

The patients in the study group had a statistically significant lower number of RBC transfusions in the 28-day period: 328 (50.5%) versus 394 (60.4%) patients received transfusions. The *p* value for this comparison was < 0.001. A Kaplan-Mier plot showed that the time to first transfusion started to diverge at the end of the first week following randomization and progressively diverged throughout the 28-day period. The total number of RBC transfusions was lower in the rHuEPO group: 1590 versus 1963 in the placebo group. An analysis for time at risk for first transfusion showed a 19% reduction in the rHuEPO group per day alive (ratio of transfusion rates, 0.81; 95% CI, 0.79-0.83; *P* = 0.04). Those patients receiving rHuEPO had a higher mean hemoglobin level from baseline to final determination compared to the placebo group (1.32 ± 2 g/dL versus 0.94 ± 1.9 for placebo; *p* < 0.001). The threshold for transfusions was similar in the two groups. The mean hemoglobin level before transfusion was 8.53 (±1.08) g/dL in the rHuEPO group and 8.57 (±0.96) for the placebo group. In each group, only 21% of the patients received transfusions for hemoglobin >9 g/dL and Hct >27%.

The 28-day mortality rate did not differ in the two groups (14% in

rHuEPO versus 15% in placebo; $P = 0.61$). Severe adverse events were similar in both of the groups. The median hospital length of stay did not significantly differ in the two groups. There was trend toward higher readmission rates to the ICU for the placebo group compared to the study group (13.3% versus 9.8%, respectively; $P = 0.07$). Ventilator-free days did not differ between the two groups.

COMMENTARY

Anemia is a common problem in the critically ill, leading to a high number of transfusions: 35% to 50% of ICU patients receive RBC transfusions during their ICU stay (Vincent JL et al. Anemia and blood transfusion in critically ill patients. *JAMA*. 2002;288:1499–1507). RBC transfusions are not entirely benign. In addition to the obvious but rare chance of contracting such viral illnesses as human immunodeficiency virus, hepatitis B virus, and hepatitis C virus, RBC transfusions may contribute to increased mortality. The recent epidemiologic study by Vincent and colleagues showed increase in mortality as well as an increase in organ dysfunction in patients who received a greater number of RBC transfusions when compared to patients matched in organ dysfunction. Other adverse effects of transfusions include allergic reactions and the potential for immunosuppression.

Despite the increased safety of our blood supply, we have not, and likely will not, achieve a “zero” risk. Additionally, the increasing age of our population and restrictions on donors have already reduced our donor pool, and shortages of allogeneic blood are anticipated. Erythropoietin is increasingly being used to reduce the number of transfusions in ICU patients and in other settings, such as elective orthopedic surgery, in patients with end stage renal disease, and in cancer patients. Previously, Corwin and colleagues in 1999 demonstrated a significant decrease in the total number RBC transfusions and an increase in Hct in a small group of critically ill patients given high doses of rHuEPO compared

to those given a placebo (Corwin HL et al. Efficacy of recombinant human erythropoietin in the critically ill patient: a randomized, double blind, placebo-controlled trial. *Crit Care Med*. 1999;27:2346–2350).

In this study, the authors provide further evidence to support the use of rHuEPO in the long-term ICU patient: fewer patients treated with weekly erythropoietin required transfusions compared to placebo, with an 19% reduction in total number of RBC units transfused; the final Hgb and Hct levels were higher in the study group. However, the magnitude of the reduction was significantly lower than in the previous study. The authors suggest that the shorter follow-up period in the present study may account for this difference, as well as the lower dose of rHuEPO (about half the amount given in the previous trial).

There has been a trend in recent years to try a more conservative approach to transfusion in critically ill patients. In 1941 in a paper ironically titled “Anesthesia in cases of poor surgical risk: some suggestions for decreasing the risk,” Adams and Lundy recommended transfusions for perioperative patients if the hemoglobin concentration was in the range of 8.0 to 10.0 g/dL. Since then, the values of 10 and 30 for Hgb and Hct, respectively, have remained an unwritten rule. In the Canadian survey in 1998, Hebert and colleagues described a wide range of thresholds for RBC transfusions, with a large proportion of critical care physicians using 10 g/dL of hemoglobin as a cut-off (Hebert P et al. A Canadian survey of transfusions practices in critically ill patients. *Crit Care Med*. 1998;26:482–487). Subsequently, a number of studies have shown that a more restrictive approach to RBC transfusions is at least as effective and safe as a more traditional approach. Hebert and colleagues found that maintaining a hemoglobin level between 7.0 and 9.0 g/dL and a transfusion threshold of 7.0 g/dL had a lower mortality than maintaining a Hgb level between 10.0 and 12.0 g/dL and a transfusion threshold at 10.0 g/dL,

especially in patients with an APACHE II score <20 and among patients younger than 55 (Hebert P et al. A multicenter, randomized, controlled trial of transfusion requirements in critical care. *N Engl J Med*. 1999;340:409–417). The transfusion threshold in this study was a Hgb of 8.5, which is similar to the levels reported in the literature in the United States and in Europe. It is disappointing that this threshold has not changed, despite the vast evidence that indicates that lower Hgb levels are safe and well tolerated in the majority of critically ill patients, perhaps with the exception of patients with severe cardiac dysfunction and/or active ischemia.

This is the largest study to date establishing the efficacy of rHuEPO in critically ill patients to reduce the number of RBC transfusions. No significant differences in morbidity and mortality were detected, despite the large number of patients enrolled. Only 19% of all eligible patients were approached for consent, and 13% participated in the study. This raises the question as to whether the results are generalizable to all ICU patients.

In analyzing the cost of using rHuEPO, the authors showed that the average cost of 40,000 units of rHuEPO is approximately \$400 and the average cost of each unit of RBCs is \$300 to \$400. Here the average patient received two to three doses to avoid one unit of RBC transfusion. While the cost of rHuEPO is higher, savings, if you would like to call it that, may be seen in decreased allergic reactions, potential for infection, organ dysfunction, and clerical errors.

This study demonstrated that the use of rHuEPO contributes to transfusion independence in critically ill patients. However, simple practices, such as adhering to lower transfusion thresholds and minimizing blood drawing, are clearly safe and less expensive. Combining these simple steps with the use of erythropoietin in long-term ICU patients would certainly significantly decrease the need for allogeneic blood transfusions in the critically ill.

Levalbuterol Versus Albuterol: A Paradox—What Costs More Costs Less

Peter Spiegler, MD, FCCP

Abstracts From Literature

SYNOPSIS: *A retrospective chart review of two seasonally matched periods examining efficacy, outcomes, and costs in hospitalized patients using nebulized levalbuterol or nebulized racemic albuterol suggests that the use of levalbuterol decreases cost of care of asthmatics and COPD patients.*

SOURCE: *Truitt T et al. Levalbuterol compared to racemic albuterol. Efficacy and outcomes in patients hospitalized with COPD or asthma. Chest. 2003;123:128–135.*

In this study, the investigators performed a chart review of all patients admitted to their institution with a diagnosis of asthma or COPD during two matched seasonal periods. During July through December of 1998, racemic albuterol was the standard β -agonist used at their facility, and during July through December of 1999, levalbuterol was the standard agent used. The primary endpoint examined was the number of nebulizer treatments required. The secondary endpoints included changes in pulmonary function, length of stay (LOS), and pharmacy and hospitalization costs.

There were 38% fewer nebulizer treatments given to patients treated with levalbuterol compared to racemic albuterol (19 versus 30.8 treatments). This value was more pronounced in asthmatic patients than in those with COPD. As a corollary, less ipratropium bromide was given as concomitant therapy in the levalbuterol group. The total number of nebulizer days was lower in the levalbuterol group (3.9 versus 5.5; 29% reduction). There was no significant difference in the need for rescue nebulizer therapy during hospitalization in either group.

There was a strong but not statistically significant trend toward shorter hospital stay in the levalbuterol-treated patients (4.7 versus 5.6 days). Furthermore, readmission rates at 30 days were lower in the levalbuterol group. Cost analysis was performed using 1999 *Red Book* wholesale prices for nebulizer costs and hospital stay costs using maximum reimbursable Medicare payments. The cost of respiratory therapy could not be independently as-

sessed. Mean total hospital costs were not significantly different between the two periods.

COMMENTARY

Racemic albuterol is an equimolar mixture of *R*- and *S*-albuterol. The *R* enantiomer of albuterol (levalbuterol) accounts for all of the bronchodilatory action of albuterol. *S*-albuterol has no β -adrenergic activity, but it increases intracellular calcium levels (Yamaguchi H et al. *S*-albuterol exacerbates calcium responses to carbachol in airway smooth muscle cells. *Clin Rev Allergy Immunol.* 1996;14:47–55). Studies of *S*-albuterol have shown mixed results, with some showing increased bronchial hyperreactivity (Perrin-Fayolle M. Differential responses of asthmatic airways to enantiomers of albuterol. Implications for clinical treatment of asthma. *Clin Rev Allergy Immunol.* 1996; 14:139–147), while others have shown no effect on bronchial reactivity (Cockcroft DW. Effect of single doses of *S*-salbutamol, *R*-salbutamol, racemic salbutamol, and placebo on the airway response to methacholine. *Thorax.* 1997; 52:845–848). Because of reports of increased hyperreactivity, increased eosinophil recruitment, and the longer half-life of *S*-albuterol, levalbuterol has been purported to be safer than racemic albuterol.

In a large, randomized, controlled trial comparing levalbuterol to racemic albuterol, there were more side effects seen with increasing doses of each, but there was no difference between albuterol and levalbuterol at equivalent doses (Nelson H et al. Improved bron-

chodilation with levalbuterol compared to racemic albuterol in the treatment of asthma in pediatric patients. *J Allergy Clin Immunol.* 1998;102:943–952). Levalbuterol produced greater initial bronchodilation after the first dose than racemic albuterol, but this difference was not apparent after 4 weeks of treatment. This study essentially demonstrated equivalence of the two therapies.

In view of the fact that there is no clear superiority of levalbuterol compared to albuterol, this study examined whether use of levalbuterol afforded a cost savings. 2002 *Red Book* wholesale costs were \$0.44 per unit dose for albuterol and \$2.17 for levalbuterol. Despite this, the authors hypothesized that the less frequent dosing of levalbuterol as well as the theoretical advantages of levalbuterol may lead to decreased overall cost by reducing pharmacy cost, utilization of respiratory therapy services, and hospitalization costs.

The decrease in the number of nebulizer treatments when levalbuterol was used as opposed to albuterol is not surprising considering that it is dosed every 8 hours instead of every 4 hours. There was, however, less concomitant ipratropium use, and there was a decrease in the total number of nebulizer days, suggesting that levalbuterol may be more effective. However, since this is a retrospective chart review and not a controlled trial, this is merely speculative. The decreased use of ipratropium likely represents an issue of different prescribing practices. The difference in nebulizer days may reflect differences in physician practice patterns, which occurred between the two time periods.

An analysis of cost showed nearly a 50% reduction in nebulizer costs in the levalbuterol group. Part of this may be due to the decreased use of ipratropium in these patients and may be independent of any potential benefits of levalbuterol. Hospitals often contract to obtain albuterol at costs significantly lower than *Red Book* pricing, which needs to be calculated into any cost analysis that a hospital performs. The cost of respiratory therapy services is often not directly added to the cost of hospitalization. However, it can be calculated given the cost of therapist time per treatment (hourly salary divided by the standard of 26 minutes per treatment). Adding to this the cost of the

medication will give the total cost of administering each treatment (using *Red Book* prices and an hourly rate for salary plus benefits of \$31.25 gives a cost of \$13.98 for albuterol and \$15.75 for levalbuterol). Therefore, the cost is slightly more for levalbuterol but the therapist can treat twice the number of patients assuming an every eight- versus every four-hour schedule. This may lead to better therapist utilization and possibly a decrease need for personnel, which may translate into indirect savings. As such, this means that individual respiratory therapy divisions should perform their own cost analysis. Any cost savings of such, however, would not lead to a direct reduction in the cost of hospitalization.

The decrease in LOS by almost one day is intriguing, but the relationship of this finding to levalbuterol is uncertain. Is levalbuterol more efficacious than racemic albuterol? Does therapy with levalbuterol lead to more rapid resolution of exacerbations? Does use

of racemic albuterol lead to more side effects because of its increased systemic β -adrenergic activity (atrial arrhythmias), which can increase LOS? Unfortunately, the lack of a control group makes these questions difficult to answer. No mention is made of side effects of either therapy here. Many factors that are uncontrolled for may account for the difference in LOS. Annual differences in respiratory infections may affect severity of illness and length of hospitalization. Influenza rates were similar for both time periods (Update: Influenza activity: United States and worldwide, 1999–2000 season and composition of the 2000–01 influenza vaccine. *MMWR Recomm Rep.* 2000;49:375–81.). Infections with atypical organisms may also change on an annual basis (Layoni-Milon MP, Valette M, Luciani J, et al. Incidence of upper respiratory tract mycoplasma pneumoniae infections among outpatients in Rhone-Alpes, France, during five successive winter periods. *J Clin*

Microbiol. 1999;37:1721–6.), and this may contribute to any differences seen between the two time periods. Practice patterns may also have changed over the study period, accounting for change in the LOS.

Currently, a randomized, controlled trial is underway which should help answer these questions. When two competing medications exist, the decision of which to use should be based primarily on which is the better drug. With racemic albuterol and levalbuterol, superiority of one or the other has not been clearly demonstrated. In the absence of a difference in efficacy, it is reasonable to examine the cost of each agent. The per-unit price clearly favors racemic albuterol. The total cost of each, however, is more difficult to quantify. This study helps to clarify the issues involved. Unless superiority of levalbuterol is subsequently demonstrated, respiratory therapy divisions should conduct their own cost analysis based on their needs to determine which will provide savings.

Pulmonary-Artery Catheterization in High-Risk Surgical Patients: Time to Pull That Catheter

Anil Mattoo MD, & Maritza L. Groth, MD, FCCP

Abstracts From Literature

SYNOPSIS: *The use of pulmonary-artery catheters to guide therapy affords no benefit over standard therapy in elderly high-risk surgical patients requiring intensive care.*

SOURCE: Sandham JD et al. *A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients.* *N Engl J Med.* 2003;348:5–14.

The study by Sandham and colleagues was a multicenter, randomized-controlled trial (RCT) comparing goal-directed therapy guided by pulmonary artery catheters (PACs) with standard care, without the use of the catheter, in patients undergoing major surgery. Eligible patients were >60 years of age and were scheduled for major abdominal, thoracic, vascular, or hip fracture surgery, either urgently or electively. They had to be

American Society of Anesthesiologists (ASA) class III or IV. The use of central venous catheters (CVCs) to measure central venous pressure (CVP) was allowed in the standard care group. Patients in the study group had a PAC placed before surgery, and the treatment was directed to physiologic goals established by the investigators before the study began. Goals, in order of priority, were oxygen delivery index (ODI) of 550 to 600 mL/min/m², car-

diac index (CI) of 3.5 to 4.5 L/min/m², mean arterial pressure (MAP) of 70 mm Hg, pulmonary capillary wedge pressure (PCWP) of 18 mm Hg, heart rate (HR) <120 beats/min, and hematocrit >27%. Therapy to achieve these goals included fluid loading, inotropic agents, vasodilator therapy, vasopressors for hypotension, and blood transfusion for a hematocrit <27%. Cross-over of patients in the standard-care group to the use of a PA catheter was not permitted.

Low-dose subcutaneous heparin was recommended for thromboprophylaxis before and after surgery. Clinical data, including New York Heart Association (NYHA) functional class, Goldman Cardiac Risk Index (GCRI), vital capacity (VC), and forced expiratory volume in one second (FEV₁), were recorded at enrollment. Clinical and outcome data were obtained 24 hours after surgery and weekly during the ICU and hospital stay, until death or hospital discharge. Vital status was ascertained 6 and 12 months after randomization by telephone contact with patients, family members, surgeons, or family physicians, or through hospital or provincial records. A data safety monitoring committee conducted a safety analysis after

the enrollment of 800 patients and another after the enrollment of 1600 patients. The primary outcome was in-hospital mortality from any cause. Secondary outcomes were 6-month mortality, 12-month mortality, and in-hospital morbidity from various conditions including myocardial infarction (MI), left ventricular failure (LVF), arrhythmias, pneumonia, pulmonary embolism (PE), renal insufficiency, liver insufficiency, or sepsis. Random assignment of patients to treatment groups and assessment of outcomes on the basis of a priori definitions was performed in a blinded manner. Two observers who were unaware of the treatment-group assignments adjudicated all outcomes except death.

The study screened 3803 patients between March 1990 and July 1999. Of these, 1994 patients were randomized, 997 each to the PAC group and the standard care group. The baseline characteristics of the patients were similar in both groups. 945 patients (94.8%) in the standard-care group received the planned therapy and 52 did not. The reasons were lack of an available ICU bed (9 cases), the lack of an available operating room (9 cases), withdrawal of consent (9 cases), other reasons (3 cases), and crossover to use of a PAC (24 patients). In 12 cases, the treating physician elected to use a PAC. In the study group, 939 patients (94.2%) received the planned therapy and 58 did not. The reasons included lack of an available ICU bed (5 cases), lack of an available operating room (20 cases), withdrawal of consent (23 cases), failure of the PAC (5 cases), and other reasons (5 cases).

The median length of stay (LOS) in the hospital was similar in the two groups (10 days; interquartile range 7 to 15). In-hospital mortality was similar in the two groups; 77 patients in the standard care group (7.7%) compared with 78 patients in the PAC group (7.8%). At 6 months, the survival rate in the standard treatment group was 88.1% and 87.4% in the study group. At 12 months, the numbers were 83.9% and 83.0%, respectively, in the two groups. The estimated difference in survival was -0.7% (95% confidence interval, -3.6 to 2.2) at 6 months, with negative survival differences favoring standard care and -0.9% (95% confidence interval, -4.3 to 2.4) at 12 months. The adjusted risk ratio for death in the PAC group compared with the standard care group was 1.0 (95% confidence interval, 0.7 to 1.3). There was no evidence of variation in

treatment effect according to center or according to baseline characteristics. Subgroup analysis of in-hospital mortality according to ASA class risk, type of surgery, sex, age, and NYHA class yielded results similar to those of the primary analysis. Morbidity rates also were similar in the two groups, except that there was a higher incidence of PE in the PAC group: 0 events in the standard-care group versus 8 events (0.8%) in the in the study group ($P = 0.004$). Thromboprophylaxis with unfractionated or low-molecular-weight heparin was used in 906 patients in the standard-care group (90.9%) and 878 patients in the catheter group (88.1%; $P = 0.05$). The incidence of MI, LVF, arrhythmias, hepatic insufficiency, sepsis from the PAC or CVC, and pneumonia did not differ significantly between the groups. Fifteen patients in the PAC group (1.5%) had one or more adverse effects of the use of the catheter (two cases of hemothorax, three pulmonary hemorrhages, one pulmonary infarction, three inadvertent punctures of a major artery, and eight cases of pneumothorax). CVCs were placed in 769 patients in the standard-care group (77.1%). Five of these patients (0.7%) had an adverse event related to the catheter placement (inadvertent puncture of a major artery in one patient and pneumothorax in four patients). More patients in the PAC group received inotropic agents (48.9% versus 32.8%; $p < 0.001$), vasodilators (8.5% versus 3.9%; $p < 0.001$), antihypertensive medication (25.5% versus 16.9%; $p < 0.001$), packed red cells (56.6% versus 47.0%; $p < 0.001$), and colloids (54.8% versus 47.7%; $p < 0.002$) indicating that the study protocol resulted in differential treatment in the two groups.

COMMENTARY

Lewis Dexter first introduced the PAC in 1945. Initially, its use was restricted to measure pressures and oxygen content in the right heart chambers, thus making it possible to diagnose a wide variety of congenital heart lesions. In 1947, Dexter and his colleagues extended its use to measure PA wedge pressure by positioning a PAC in a distal branch of a pulmonary artery branch. They assumed that, in the absence of pulmonary venous disease or mitral valve disease, the pressure recorded in the wedge position reflected the filling pressure in the left ventricle. Until 1970, PACs were used exclusively by cardiologists in the car-

diac catheterization laboratory; the risks associated with the procedure seemed minimal compared to the enormous benefits of detecting specific congenital and valvular cardiac lesions amenable to surgical correction. In 1970, Swan and coworkers demonstrated that the PAC could be placed at the bedside without a fluoroscope, using a specially designed balloon-tipped catheter. They also extended the use of the PAC beyond diagnostic purposes: to guide therapy to optimize fluid management in critical illness, including acute myocardial infarction (MI). Soon after the publication by Swan and coworkers the balloon tipped catheter became commercially available to be used in ICUs. The indication for use of the PAC shifted from diagnosis to therapy. It is currently estimated that more than 1.5 million PACs are placed annually in the United States, and the annual costs associated with their use exceeds \$2 billion a year.

Despite the widespread use of the PAC, the indications for placement, the interpretation of the data, and the goals for therapy directed by it remain unclear. It has been assumed that the therapeutic decisions based on the hemodynamic data obtained from the PAC improved patient outcome. However, this has never been proven. On the contrary, recent evidence suggests that the use of PACs may be associated with increased morbidity and mortality. Unfortunately, the widespread use of PACs and the belief that they are beneficial has made it difficult to perform a RCT. Physicians cannot ethically participate in such a trial or encourage a patient to participate if convinced that the procedure is truly beneficial. As a result, in the absence of RCTs of PACs, effectiveness has only been suggested by observational studies. The probable lack of benefit of the PAC was anticipated in 1980 (Spodick DH). Physiologic and prognostic implications of invasive monitoring; undetermined risk/benefit ratios inpatients with heart disease. *Am. J. Cardiol.* 1980;46:173-175) and has been emphasized since 1983 (Robin ED). The cult of the Swan-Ganz catheter: overuse and abuse of pulmonary flow catheters. *Ann Intern Med.* 1985;103:445-449). In 1987, Gore and colleagues demonstrated a higher mortality in patients with acute MI with CHF, hypotension, or cardiogenic shock treated with PACs (Gore JM et al. A community-wide assessment of the use of pulmonary artery catheters in patients with acute myocar-

dial infarction. *Chest*. 1987;92:721–727). A number of subsequent articles recommended a moratorium on the use of PACs. Skeptics of the Gore study emphasized that since the study was not an RCT, it was possible that the higher mortality rate in patients treated with a PAC could be due to the fact that they were sicker than the patients who were not catheterized.

In 1996, Connors and coworkers published the results of an observational study involving 5735 critically ill medical and surgical patients (Connors AF Jr. et al. The effectiveness of right heart catheterization in the initial care of critically ill patients. *JAMA*. 1996; 276:889–897). Since the previous observational studies had been criticized for not adjusting for the treatment selection bias in using or withholding a PAC (also called confounding by indication), the study used a “propensity score” to account for it. The propensity score, described by Rosenbaum and Rubin, is a powerful method of accounting for the variables that independently affect the decision to use or withhold the PAC treatment. The study concluded that despite adjustment for treatment selection bias, PAC use was associated with increased mortality and increased utilization of re-

sources. This study further worsened the chaos in the medical community regarding the use of pulmonary artery catheters. It was widely accepted that there was equipoise for randomized controlled clinical trials.

This is the first RCT of this kind. The authors have demonstrated that the use of PACs to optimize hemodynamics in high-risk patients does not improve outcomes and may be associated with greater morbidity. The study lends further credence to the nonrandomized studies mentioned earlier. Several possible explanations for the above mentioned findings could be postulated. First, physicians may not have properly used the information obtained from PACs during surgery and the postoperative period. Iberti and colleagues in a multicenter study observed that physicians’ understanding of the PAC data are extremely variable (Iberti TJ et al. A multicenter study of physicians’ knowledge of the pulmonary artery catheter. *Pulmonary Artery Catheter Study Group*. *JAMA*. 1990;264:2928–2932). Additionally, several reports have demonstrated that increasing CI and oxygen delivery do not improve outcomes and may even be detrimental in critically ill patients (Hayes MA. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med*. 1994;330:1712–1722). Also, as suggested by

the report from the Study to Understand Prognosis and Preferences for Outcomes and Risks of Treatment (SUPPORT), by Connors and colleagues, the PAC may be a marker for an aggressive style of care that contributes to worse outcomes. It is obvious that any invasive procedure carries some risk of adverse outcomes. Although in this study the extent of morbidity due to PE in the study group was small, the results must be interpreted in the light of the 1.5 million patients who receive PACs in North America annually. This would translate into 12,000 additional PEs annually.

This study must be considered a landmark in research in critical care in that it demonstrates the feasibility of conducting large, adequately powered, multicenter, controlled trials of PAC that would not have been possible before. Sandham and colleagues have demonstrated that the use of PACs to guide perioperative care of elderly, high-risk patients who undergo elective or urgent major surgery does not improve outcomes compared with standard care in the ICU. Whether the results of this trial extend to other groups of patients in the ICU such as those with acute lung injury or circulatory or septic shock remains to be seen. This study will certainly foster new attempts to address this important question in future randomized controlled clinical trials.

Lung Cancer Screening: Can We Afford It?

Terence K. Trow, MD, FACP, FCCP

Abstracts From Literature

SYNOPSIS: *When all parameters are considered, projections by a computer-simulated model predict that helical computed tomography screening for lung cancer in a high-risk population is not cost effective at the present time.*

SOURCE: *Mahadevia PJ et al. Lung cancer screening with helical computed tomography in older adult smokers. A decision and cost-effectiveness analysis. JAMA. 2003;289:313–322.*

For decades, efforts to establish a societally responsible approach to lung cancer screening have been earmarked by controversy. This study by Mahadevia and colleagues promises to feed the controversy still. Ambitious and comprehensive in in-

tent, this decision and cost-effectiveness analysis uses a hypothetical 100,000 population base of 60-year-old smokers followed with helical CT scans annually for 20 years. Fifty-five percent of this simulated population is male and 45% female. A mathematical

Markov model incorporating simulated cohorts of active smokers, “quitting” smokers, and former smokers is used to compare their journey through 20 years of screening to similar cohorts who did not undergo CT screening. To construct their computer model, the authors use probabilities garnered from the Surveillance, Epidemiology, and End Results (SEER) national cancer data base, as well as the latest published literature results. Parameters such as adherence or nonadherence to screening, probability of indeterminate nodule detection, stage shift expectation inherent in CT screening, incidence of lung cancer histologic subtypes, cost of nodule evaluation, as well as allowance for length-time, lead-time, and overdiagnosis biases are included in their base-case analysis. In addition, flexible sensitivity analysis that allows alteration in probability ranges for those parameters felt likely to be most influential were carried out

to skew analysis "in favor" of screening. These parameters included age at first screening, length of follow-up, degree of nonadherence, stage shift expected, and anxiety about indeterminate nodules.

Using this model Mahadevia and colleagues determined that 553 fewer lung cancer deaths (13% lung cancer mortality reduction) would be expected in the screened cohort of current smokers, with 1186 false-positive invasive procedures required per 100,000 persons. This was achieved at a cost of \$116,300 per quality-adjusted life-year (QALY) gained. When reformed smokers were examined, costs were even higher at \$558,000 and \$2,322,700 QALY gained for "quitting" and former smokers, respectively. Even when the most favorable probabilities were simultaneously assumed for all influential parameters, the screening of active smokers would still cost \$42,500 per QALY gained. Based on these findings, the authors do not advise direct-to-consumer marketing of helical CT to screen for lung cancer.

COMMENTARY

Currently, several large prospective studies of the merits (and potential harms) of low-dose CT screening of at-risk individuals are underway (Boughton B. Large screening trial launched by NCI. *Lancet Oncol.* 2002;3:647. Kramer BS. Spiral computed tomography screening: study begins to determine efficacy in lung cancer prevention. *West J Med.* 2001;174:230-231) It will be a decade or longer before definitive data from "real-life" scenar-

ios are available. Proponents (Henschke CI et al. CT screening for lung cancer. *Rad Clin North Am.* 2000;38:487-495. Miettinen OS. Screening for lung cancer: can it be cost-effective? *Can Med Assoc J.* 2000;162:1431-1436) have appealed to our "intuition" and argued strongly for the role of CT screening in our practice now. This is, of course, predicated on the assumption that detection of smaller tumors, by definition, affords better survival. However, as Patz and coworkers point out (Patz EF et al. Screening for lung cancer. *N Engl J Med.* 2000;343:1627-1632), although several studies suggest that patients with T1 lesions do better than those with T2 lesions, there are decidedly little data correlating tumor size with survival in patients with T1 lesions. Some evidence even argues that detection of smaller nodules does not impact on survival (Heyneman LE et al. Stage distribution in patients with a small (*Cancer.* 2001;92:3051-3055; Patz EF et al. Correlation of tumor size and survival in patients with stage IA non-small cell cancer. *Chest.* 2000;117:1568-1571; Martini N et al. Incidence of local recurrence and second primary tumors in resected stage I lung cancer. *J Thorac Cardiovasc Surg.* 1995;109:120-129). To this end, studies such as Mahadevia and coworkers' that underscore the high cost (both emotionally and fiscally) of helical CT screening, remind us to be conservative in our acceptance of technology before proof of its overall merit to society exists.

The investigators are to be commended on the painstaking efforts that went into assembling the best outcomes data available for use in their

model, as well as the flexible sensitivity analysis that allowed "best case" scenario data. While it is not even clear if CT screening is effective in altering survival yet (Patz EF et al. Screening for lung cancer. *N Engl J Med.* 2000;343:1627-1632), Mahadevia and colleagues emphasize that even if it is, it may be too expensive to employ. Proponents of helical CT screening for lung cancer have offered more emotional but less rigorous cost-effective analyses (Miettinen OS. Screening for lung cancer: can it be cost-effective? *Can Med Assoc J.* 2000;162:1431-1436) that imply costs of \$10,000 per life-year saved. If correct, their projections would compare favorably to screening programs already in place for cervical (Fahs MC et al. Cost effectiveness of cervical cancer screening for the elderly. *Ann Int Med.* 1992;117:520-527) and breast cancer (Mushlin AI, Fintor L. Is screening for breast cancer cost-effective? *Cancer.* 1992;69:1957-1962).

It is worth pointing out that cost-effective analyses are intrinsically dependent on assumptions made and are only as good as those baseline assumptions. Factors such as improvements in volumetric assessment of nodule changes, variability in individual preferences that define "quality of life," probable decreases in the cost of CT screening that are likely to occur, and future changes in treatment efficacy cannot be easily reflected in any mathematical model. To this end, studies such as this one are limited by their very nature. Nonetheless, with the data currently available to us, their model raises valid concerns with the advisability of a national screening program.