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INSIDE

Shorter Antibiotic Course Effective in Ventilator-Associated Pneumonia

ABSTRACT & COMMENTARY

VENTILATOR-ASSOCIATED PNEUMONIA (VAP) REMAINS A DIFFICULT problem in critically ill patients, both in diagnosis and treatment. Recent improvements in diagnosis include using quantitative culture methods to help differentiate colonization from active infection. Once the diagnosis of VAP is confirmed, appropriate antibiotics are usually given for 14-21 days. This prolonged exposure to antibiotics may contribute to the development of bacterial resistance and may not improve resolution of the pulmonary infection. Some clinicians (myself included) believe that a shorter course of therapy is appropriate. In this multi-institutional, prospective study, an 8-day antibiotic treatment course was compared to a 15-day treatment in patients with VAP. Diagnosis of VAP was made using conventional criteria, but it was confirmed with quantitative cultures obtained by protected brush samples (at least 10^3 colony-forming units [cfu]/mL) or from bronchoalveolar lavage (at least 10^4 cfu/mL) in adult patients receiving mechanical ventilation for at least 48 hours. There was no difference in mortality (18.8% in 8-day group vs 17.2% in 15-day group), length of stay, or relapse rate, but those patients receiving 15 days of therapy had a much higher chance of having a multiresistant organism if they relapsed or developed a secondary infection (62% vs 42.1%).

This large study screened more than 1100 patients and enrolled 402 patients from 51 ICUs in France between May 1999 and June 2002. Entrance criteria excluded those with early onset VAP (which may be more sensitive to antibiotics), those expected to die from other causes, those who were immunosuppressed from disease or medication, those on long-term antibiotic treatment for extrapulmonary indications, and those who were made DNR by their attending physicians. VAP was diagnosed based on a new and persistent infiltrate on chest radiograph following at least 48 hours of mechanical ventilation and the presence of at least 1 of the following: purulent tracheal secretions, temperature of 38.3°C, and/or leukocyte count greater than 10,000. Empiric therapy had to be appropriate as confirmed by sensitivity testing

several days later to be continued to randomization. One patient withdrew consent, and 401 patients completed the study: 197 were randomized to the 8-day treatment group and 204 to the 15-day group. All completed the trial.

The primary study outcomes were death from any cause, documented pulmonary infection recurrence, and number of antibiotic-free days from diagnosis of VAP until day 28. Secondary outcome measures were mechanical ventilation-free days, organ failure-free days, multiple measures of lung failure daily, emergence of resistant infections during the entire ICU stay, and mortality at 60 days.

The groups were well matched at admission to the ICU and entry into the study (8 vs 15 days): average age (60 vs 61), male predominance (77% vs 68%), SAPS II score (45 both), duration of MV prior to VAP (13.4 vs 13.8 days), and previous exposure to antibiotics (84% vs 83%). There were fewer surgery patients in the 8-day group (31.5% vs 37.3%), but this difference was not statistically significant. Organisms responsible for the VAP were similar in both groups.

Mortality at 28 days following VAP treatment was 18.8% in the 8-day group and 17.2% in the 15-day group; at 60 days mortality, 25.4% vs 27.9%, and at hospital discharge, 32% vs 30%. There was a higher recurrence in the 8-day group if the causative organism was *Pseudomonas aeruginosa* (40.6% vs 23.8%), but this had no effect on length of stay, ventilator-free days, or mortality. Antibiotic-free days were about 50% less (no surprise) in the 8-day group over the first 28 days of treatment. Of the patients who developed recurrent pulmonary or other infections, more of the causative organisms were resistant to multiple antibiotics in the 15-day group (62.3% vs 42.1%; $P = .04$) (Chastre J, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults. A randomized trial. *JAMA*. 2003;290[19]:2588-2598).

COMMENT BY CHARLES G. DURBIN, Jr., MD

The major conclusion of this large, complicated, well-designed study is that a short course of appropriate antibiotics (8 days) is no worse than a longer one (15 days). Antibiotic usage was less, and the development of resistance was lower. The possible exception was if the infective agent was *Pseudomonas aeruginosa*, in which the shorter course was associated with a higher recurrence rate but no difference in important outcomes. The similarities between the groups in mortality, ICU length of stay, ventilator-free days, organ failure-free days, lung injury scores, oxygenation indices, and other measured variables suggest that a shorter treatment course for VAP is appropriate. In fact, treatment for less than 7 days may be even more desirable. Courses of antibiotic treatment of 48-72 hours for VAP should be studied now that this study confirms no additional benefit and a rise in risk of resistance from 15 days of treatment.

One of the strengths of this study is the use of bronchoscopic culture techniques and quantitative bacterial analysis to confirm the diagnosis of VAP. While no method appears to be perfect in this regard and controversy abounds, the quantitative methods hold the most sway among clinicians and investigators to confirm the presence of VAP. This fact and the contemporaneousness of the data make this study's findings important to current care choices. Limiting the duration of antibiotic therapy to 1 week for VAP is something that can be implemented immediately, with little concern about patient harm. Reducing unnecessary antibiotic use is an important issue for all those practicing or receiving treatment in an ICU. ■

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Pulmonary Artery Catheters Unhelpful in Shock and ARDS

ABSTRACT & COMMENTARY

Synopsis: *In this randomized, multicenter trial, early use of a pulmonary artery catheter in patients with shock, ARDS, or both did not significantly alter mortality or morbidity.*

Source: Richard C, et al, for the French Pulmonary Artery Catheter Study Group. Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome. A randomized controlled trial. *JAMA*. 2003;290:2713-2720.

This study evaluated effects on outcomes of early use of a pulmonary artery catheter (PAC) in patients with shock, mainly of septic origin, the acute respiratory distress syndrome (ARDS), or both. Subjects were patients enrolled from 36 ICUs in France over a 30-month period (January 1999-June 2001) and randomly assigned to either receive a PAC (n = 355) or not (n = 341). Patients with shock for > 12 hours or ARDS for > 24 hours were excluded to avoid studying partly resolved shock or respiratory failure. Criteria for shock and ARDS were precisely defined. Treatment was at the discretion of individual physicians. However, participating physicians agreed on the following principles: optimization of circulating blood volume, vasoactive support if needed at a mean arterial pressure of at least 60 mm Hg when fluid balance was optimized, no objective of maximization of oxygen transport, free access to echocardiography, assist control ventilation with a maximum plateau pressure of 35 cm H_2O and SpO_2 of more than 90%, and prevention of thromboembolism with low-molecular-weight heparin, if not contradicted. The 2 groups were similar at baseline.

There were no significant differences in mortality with or without a PAC at day 14 ($P = 0.70$), day 28 ($P = 0.67$), or day 90 ($P = 0.71$). At day 14, the mean number of days of organ system failure with or without use of the PAC, renal support, and vasoactive agents did not differ. At day 28, mean days in the hospital with or without the PAC, in the ICU, or mechanical ventilation use also did not differ. Overall mortality at day 28 was 60.2%. On an intention-to-treat basis, this percentage did not differ significantly between the PAC and the control group at day 28 (199 [59.4%] vs 208 [61.0%] deaths). In one center, a significant difference in mortality in favor of the PAC was observed. After adjustment for severity of illness on admission (SAPS II), this difference was no longer significant. There were few complications: arrhythmias and conduction disturbances (n = 60), arterial puncture (n = 17), hemothorax (n = 1), and knotting of the catheter (n = 6). No pulmonary embolism or deep-venous thromboembolism was recorded.

COMMENT BY LESLIE A. HOFFMAN, PhD, RN

The major findings of this study were that patients randomized to early use of a PAC did not experience adverse events, nor did they derive any benefit. Accordingly, findings of this study differ from prior observational studies that raised doubts about the safety of PAC. The present study was unique in several ways. The population was restricted to patients with shock, ARDS, or both. Most (67%) were diagnosed with septic shock. Patients with shock for > 12 hours or ARDS for > 24 hours were excluded to avoid studying partly resolved shock or respiratory failure. General goals were established, but treatment was left to the discretion of each individual physician. This decision was made because adverse results were reported from prior studies that did not use a formal protocol and lack of consensus on how to best manage hemodynamic support in this population. This choice seems reasonable, especially in view of concerns voiced as a result of the ARDSnet investigators' decision to select one treatment strategy. Protocol violations were infrequent. A PAC was inserted in 15 (4.4%) control patients, and 8 (2.4%) patients in the PAC group did not receive it because they died before insertion (n = 6) or placement was not possible (n = 2). Only 3 patients were lost to follow-up (1 PAC, 2 controls).

The major shortcoming of the study relates to its failure to meet recruitment goals. To avoid changes in practice that might influence study outcomes, the plan was to conclude the study after 18 months. Enrollment was slower than anticipated, and the study was extended to 30 months. Because enrollment continued to be slow, the study was closed 76 patients short of the enrollment goal. As such, the study was powered to detect a difference of 10%, but underpowered to detect a difference of 5%. Within these constraints, no difference was seen in mortality or morbidity.

As Richard and colleagues note, it would be unrealistic to believe that patient prognosis would be improved by use of a PAC alone. Any influence on prognosis would need to result from significant changes in treatment as a result of having the catheter. Of interest,

physicians who managed both groups had access to free echocardiography. At least one examination was performed in 64% of the PAC group and 78% of the control group. In the latter group, echocardiography was used to assess ejection fraction and with Doppler analysis to evaluate cardiac output and estimate pulmonary artery pressure and left ventricular end-diastolic pressure. This noninvasive technology may provide benefits similar to those obtained with a PAC without its inherent risks. ■

ICU Delirium Common in Older Patients

ABSTRACT & COMMENTARY

Synopsis: *Among patients aged 65 or older, 31% were delirious on admission to the ICU, and 70% experienced delirium at some time during their hospitalization.*

Source: McNicoll L, et al. Delirium in the intensive care unit. *J Am Geriatr Soc*. 2003;51:591-598.

In this study from Yale-New Haven Hospital, 118 consecutive patients aged 65 and older who were admitted to the medical ICU were evaluated using 2 different instruments for assessing delirium. Delirium was present in 31% (37/118) of the patients at the time of admission to the ICU. Only 38% (45/118) of the patients had normal mental status on admission to the ICU, and 31% of these (14/45) became delirious during their hospital stay. Delirium also occurred in 40% of patients in the post-ICU phase of hospitalization, including its persistence or recurrence in half of those who were delirious in the ICU. All told, 70% (83/118) of the patient cohort experienced delirium during the hospital stay. Patients with dementia were 40% more likely to develop delirium in the hospital than patients who were not demented on admission (relative risk, 1.4; 95% confidence interval, 1.1-1.7).

■ COMMENT BY DAVID J. PIERSON, MD

Delirium can be defined as an acute confusional state that usually occurs in the face of medical illness or the effects of drugs. It is distinguished from dementia by its acute onset, the fact that delirious patients experience an acute change in level of consciousness, and the presence of a high level of inattention. This study from the MICU of a large university teaching hospital shows that delirium is very common in older patients who require an ICU stay. If patients have evidence of dementia prior to ICU admission, they are especially likely to become delirious, according to the results of this study.

Delirium can be as distressful to patients as pain. It is all too easy for ICU clinicians to focus on physiology and "the numbers" in patients admitted to the ICU. This study points out that the patient's experience of acute illness and its predilection for inducing acute delirium should be as much on the clinician's radar screen as the physiological manifestations and their manipulation. ■

Preventing Contrast Nephropathy

ABSTRACT & COMMENTARY

Synopsis: *Meta-analysis of published clinical trials showed that a regimen of oral acetylcysteine administration along with hydration reduced the relative risk of developing contrast nephropathy by 56% among patients with pre-existing renal insufficiency.*

Source: Birck R, et al. Acetylcysteine for prevention of contrast nephropathy: Meta-analysis. *Lancet*. 2003;362:598-603.

Radiocontrast media can lead to a reversible deterioration in renal function beginning soon after administration in 10-30% of patients with underlying renal insufficiency. A number of clinical trials have evaluated the efficacy of acetylcysteine (Mucomyst) administration, along with periprocedural hydration, in preventing or reducing the severity of this complication. Because the results of these studies have been inconsistent, Birck and associates at the University of Mannheim performed a rigorous meta-analysis of published data to examine the overall effect of this agent.

Birck et al followed the guidelines of the QUORUM Group[1] in performing and reporting the results of their meta-analysis. They identified 13 studies published between 2000 and 2003 that examined the effect of acetylcysteine in preventing contrast-induced nephropathy. The most common dose of acetylcysteine given was 600 mg twice daily orally for 4 doses; however, a few trials gave more or less of the drug or administered it intravenously. The primary outcome measure was development of contrast nephropathy defined as an increase in serum creatinine of at least 0.5 mg/dL or an increase of 25% from baseline in the 48 hours following administration of contrast media.

Seven trials fulfilled all of Birck et al's predetermined criteria, reporting results from 805 patients with underlying renal insufficiency who were given 75-187 mL of intravenous contrast material. The overall incidence of contrast nephropathy in these trials was 8-28%; 4 of the 7 studies showed a significant benefit from acetylcysteine, and 3 showed no difference from hydration alone. According to the meta-analysis, the administration of acetylcysteine and hydration reduced the relative risk of developing contrast nephropathy in patients with underlying renal insufficiency by 56% (0.435; 95% confidence interval, 0.215-0.879; P = 0.02). There was no significant relationship between the relative risk of contrast nephropathy and the volume of radiocontrast material infused, or with the degree of pre-existing renal insufficiency.

COMMENT BY DAVID J. PIERSON, MD

Publication of the positive results of the first randomized, controlled, clinical trial of acetylcysteine administration to prevent contrast nephropathy[2] created quite a stir among clinicians and the medical media. Several subsequently published studies had less impressive results, and it remained unclear just how effective this therapy was. This meta-analysis, performed rigorously and according to what are currently felt to be the appropriate standards, shows that the effect appears to be real and substantial.

Although acute renal failure is an independent risk factor for mortality in hospitalized patients, contrast nephropathy is a poorly defined condition in critically ill patients. In an editorial accompanying the Birck paper,[3] Kellum points out that the clinical relevance of preventing a 0.5 mg/dL increase in serum creatinine in about half of high-risk patients receiving contrast media through the administration of acetylcysteine is uncertain in many cases. Nonetheless, acetylcysteine is a relatively safe and inexpensive drug, and its use along with appropriate hydration should be strongly considered whenever radiocontrast material is to be administered to high-risk patients. According to Kellum, patients who would potentially benefit from administration of acetylcysteine in combination with hydration include those with diabetes, cardiac, or liver disease, as well as those with pre-existing chronic renal insufficiency.

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Dedicated Medication Nurse Did Not Reduce Error Rates

ABSTRACT & COMMENTARY

Synopsis: *Use of a dedicated medication nurse had no effect on the total number of medication errors based on observations performed in medical, surgical, and mixed medical-surgical units.*

Source: Greengold NL, et al. The impact of dedicated medication nurses on the medication administration error rate: A randomized controlled trial. *Arch Intern Med*. 2003;163:2359-2367.

Medication administration is an activity prone to errors. A variety of potential causes have been posed, including the proliferation of new drugs, increased patient acuity, and increased workload due to the nursing shortage. This study was performed to determine whether use of a dedicated medication nurse would reduce error rates by allowing the nurse to focus on medication administration. The study was conducted simultaneously at an academic community hospital (hospital A) and a university teaching hospital (hospital B) over a 12-week interval. There were 2 study units at each institution. At hospital A, the 2 study units admitted either medical or surgical patients. At hospital B, both units admitted mixed medical and surgical patients. The nurses were 16 volunteers recruited from unit staff and randomly assigned to function as either a medication nurse or general nurse for a 6-week block of time. Each medication nurse received 8 hours of training. Trained observers watched and recorded all errors including those related to drug, dose, formulation, route, rate of administration, reconstitution, administration technique, and omitted drugs. Each medication nurse was responsible for 16-18 patients and general nurses an average of 6 patients.

The total error rate was 15.7% for medication nurses and 14.9% for general nurses (P = 0.84). Error rates for medication nurses were higher in about half the weeks. When the two institutions were compared, the total error rate was higher for medication nurses at hospital B (19.7%) than hospital A (11.2%) (P < 0.04) but not different for general nurses (15.0% vs 14.7%, respective-

ly). The most common medication errors were administration technique (6.4%), dose preparation (1.4%), omitted drugs (0.9%), and incorrect dosage (0.8%). There was no significant difference in errors between medication and general nurses on medical units, but there was a lower ($P < 0.01$) rate of errors for medication nurses on surgical compared to medical floors. There was no known association between the errors observed and patient outcome.

COMMENT BY LESLIE A. HOFFMAN, PhD, RN

The premise of this study was that a simple change in work design (dedicated medication nurse) and educational intervention might decrease the number of medication errors. In fact, the intervention had no effect the majority of the time. With the exception of the surgical units (where fewer medications were administered), the error rate was unchanged or tended to be higher with a medication nurse. At one time, team nursing was the predominant form of work organization, and a dedicated medication nurse was part of this work design. Team nursing was largely abandoned due to the belief that patient care is best carried out when the nurse is responsible for all aspects of patient care and can analyze patient response from a holistic perspective. In contrast, the medication nurse focuses on the process of "passing out pills" and may miss important signs and symptoms that suggest the need for a change in the plan of care.

It was interesting that significant differences in favor of the medication nurse only occurred in surgical units where the number of medications per patient is usually less. Study data support this potential, as Greengold and associates calculated the potential for error based on the number of medications administered. There were 75 opportunities per day for medical units and 48 opportunities per day on surgical units.

In commenting on their findings, Greengold et al posed 2 possible explanations for their failure to find a difference in error rates. First, there were differences in medication administration systems with the system that was judged more complex in the hospital (B) with higher error rates for medication nurses. This, however, would affect both groups. Second, they posed that there may be a threshold number of medications, activities, and patients that one nurse can manage, above which the error rate increases. Therefore, adding a medication nurse with responsibility for up to 18 patients provided no advantage. The latter explanation seems the more logical and correct for medication as well as general nurses.

Special Feature

Recruitment Maneuvers in ARDS

By Enrique Piacentini, MD, and Francisco Baigorri, MD, PhD

Mechanical ventilation (MV) is a supportive life-saving therapy in patients with acute respiratory distress syndrome (ARDS). In the last decade, the possibility that MV can produce alterations in lungs, namely ventilator-induced lung injury, has been recognized.[1] To minimize this damage, lung protective strategies to avoid the overdistension and cyclic collapse and re-opening of alveoli have been successfully used in patients with ARDS receiving MV.[2,3] Recruitment maneuvers (RM) consisting of sustained inflation to open the collapsed alveolar units have been proposed as an adjunct in the ventilatory management of patients with ARDS.[4,5] However, in most instances, lung recruitment and overdistension occur simultaneously at higher intrathoracic pressure than when RM are not used.[6] Moreover, whether the effect of RM on healthy parts of the lung might induce triggering of cellular mechanisms of injury is still unknown. The objective of this essay is to briefly review the implications of experimental and clinical studies of RM in ARDS patients.

Experimental Evidence on Recruitment Maneuvers

The beneficial effects of RM have been demonstrated in animal models of alveolar collapse induced by surfactant depletion, such as saline-lavaged rabbit lungs. In this model, an improvement in respiratory system compliance and oxygenation were observed after RM.[7] However, some data suggest that RM have different effects depending on the type of lung insult and also on the use of different combinations of tidal volume and positive end-expiratory pressure (PEEP). Whether RM are necessary to prevent alveolar collapse when optimal PEEP is used remains controversial. Van der Kloot and colleagues[8] studied the effects of RM on gas exchange and lung volumes in 3 experimental models of acute lung injury: saline lavage, oleic acid infusion, and induced pneumonia. After RM, oxygenation improved only in the surfactant-depletion group when low PEEP was used. At high PEEP, RM had no effect in any of the ARDS models tested.[9]

Recruitment Maneuvers in ARDS Patients

Since the reports of Amato and associates[2] and the Consensus Conference on ARDS,[10] the application of periodic RM in patients with ARDS has gained acceptance among clinicians—although controversy still remains. Recruitment improved oxygenation, intrapulmonary shunt, and lung mechanics, but these effects were lost when the patients were ventilated with high PEEP, suggesting that high PEEP better stabilized alveoli and prevented lung volume loss. In the same line, beneficial effects on oxygenation were observed, but only if PEEP was increased after RM.[11,12]

Other studies have shown a modest and variable effect of RM on oxygenation when ARDS patients are ventilated with high PEEP. Richard and colleagues[13] demonstrated decreased oxygenation when tidal volume was decreased from 10 mL/kg to 6 mL/kg with PEEP set above the lower inflection point of the pressure-volume curve. However, increasing PEEP and RM prevented alveolar derecruitment, and RM performed in patients already ventilated with high PEEP had minimal effects on requirements for oxygenation support. Similarly, Villagrá and associates,[14] studying the effect of RM superimposed on a lung-protective strategy, found no effect on oxygenation regardless of the stage of ARDS; furthermore, in some patients, venous admixture increased during RM.

In summary, RM can be useful to improve oxygenation in patients receiving MV with low levels of PEEP and low tidal volumes. However, in patients with ARDS receiving MV with high PEEP levels, the beneficial effects of RM were not observed.

Lung Infection and Mechanical Ventilation

Recent studies suggest that the detrimental effect of MV can be aggravated when lungs are infected or primed with endotoxin. Experimental studies demonstrated the strong effect of both MV and infection on the lung because they seem to act synergistically when causing alveolar damage.[15] These experimental studies suggest that for a similar lung infection, the presence of MV (cyclic positive intrathoracic pressure) favors greater bacterial burden and enhanced bacterial translocation from the lung into systemic circulation. These effects are particularly important when using ventilatory strategies that apply large transpulmonary pressures (high tidal volume and/or high alveolar pressures without PEEP)[16] and are partially attenuated when lung-protective ventilatory strategies are used.[17] Recruitment maneuvers appear to exert little effect on consolidated lung areas but can cause overdistension in some lung regions where bacteria are compartmentalized on the site of infection or colonization.

Conclusions

Considerable uncertainty remains regarding the use of RM in humans with ARDS. RM may have a role in patients with early ARDS and normal chest wall mechanics since there is great potential for alveolar recruitment, and after disconnections from the ventilator where sudden loss of lung volume promotes alveolar instability and derecruitment. Recommendations to use RM as adjuncts during lung protection ventilatory strategies seem unnecessary since sustained improvements in lung function have not been found when both strategies are combined. The presence of lung infection must be considered a major limitation for aggressive RM since translocation of bacteria and occurrence of systemic sepsis have been demonstrated in animal models. Ultimately, then, the use of RM cannot be recommended, and if used, RM should be restricted to an individualized clinical decision or as a last resort to improve oxygenation and lung mechanics in a severely hypoxemic ARDS patient. ■

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CME / CE Questions

16. Ventilator-associated pneumonia caused by bacteria should be treated with appropriate antibiotics:
a. for a minimum of 15 days to improve mortality.
b. for no more than 8 days to prevent bacterial resistance.
c. for a minimum of 15 days to prevent recurrence of the primary infection.
d. for no more than 48 hours with broad-spectrum agents to prevent fungal overgrowth.
e. but treatment duration has no impact on mortality or length of stay.

17. When outcomes were compared for patients with shock or ARDS managed with and without a pulmonary artery catheter (PAC), outcomes included:
a. lower mortality in the PAC group.
b. fewer mean organ system failure days in the PAC group.
c. fewer complications in patients who did not received a PAC.
d. no difference in any measure of mortality or morbidity.
e. lower 28 day but not 14 day mortality.

18. Overall, what proportion of patients 65 or older experienced delirium during their acute hospital stay?
a. 40%
b. 50%
c. 60%
d. 70%
e. 80%

19. Patients with which of the following conditions are at high risk for contrast nephropathy?
a. Diabetes
b. Cardiac disease
c. Liver disease
d. Renal insufficiency
e. All of the above

20. The application of periodic recruitment maneuvers in patients with ARDS:
a. has a beneficial effect only in those patients receiving MV with high PEEP levels.
b. is particularly recommended in patients with lung infections.
c. should be recommended instead of lung protection ventilatory strategies.
d. improves oxygenation in those patients receiving MV with low PEEP and low tidal volume.
e. All of the above

Answers: 16.(b); 17.(d); 18.(d); 19.(e); 20.(d)

CME / CE Objectives

After reading each issue of *Critical Care Alert*, readers will be able to do the following:
- Identify the particular clinical, legal, or scientific issues related to critical care.
- Describe how those issues affect nurses, health care workers, hospitals, or the health care industry in general.
- Cite solutions to the problems associated with those issues.

In Future Issues:

High FIO_2 Deleterious in Acute Asthma