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Critical Care [ALERT]

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SPECIAL FEATURE

Patients Rarely Sleep in the ICU

By James McFeely, MD

Medical Director, Critical Care Units, Alta Bates Summit Medical Center, Berkeley, CA

Dr. McFeely reports no financial relationships relevant to this field of study.

Lack of quality sleep is a ubiquitous problem for ICU patients. Recent recognition of the importance of sleep will be reflected in the next revision of the Society of Critical Care Medicine's Pain, Agitation, and Delirium (PAD) Guidelines. The 2017 revision will now be called PAD-ES, with the E standing for exercise and the S for sleep. Increasing the amount of deep sleep is one of the two most important treatments for delirium, as sleep deprivation affects cognitive functioning and is associated with increased frequency of delirium. Sleep deficit also is associated with adverse physiologic changes. For example, sleep deprivation has been associated with increases in norepinephrine and cortisol levels as well as a decrease in growth hormone levels and increased insulin resistance.[1] These changes are associated with worse outcomes in the ICU. Reduction in quality sleep also can result in decreases in inspiratory muscle endurance.[2] Understanding the mechanisms of sleep deprivation in the ICU may help clinicians modify some of these factors to promote better quality sleep.

Patient-specific risk factors for sleep deprivation in critically ill patients include type and severity of underlying disease, pain, stress, anxiety, and the underlying pathophysiology of their acute illness.[3] Despite the need to learn more about this topic, it is very difficult to conduct quality sleep research in the ICU. While polysomnography is the gold standard, traditional electroencephalogram (EEG) findings of sleep are not routinely present in ICU patients. EEGs also require skilled personnel to apply and interpret the data. As a result, there are very few high-quality sleep studies in this patient population. Patients in the ICU have marked deficits in slow wave sleep (stages 3 and 4), while rapid eye movement (REM) sleep is often completely abolished. The majority of patients' sleep is stage 2, and their sleep cycles are frequently very fragmented.[4]

Even without rigorous sleep studies, we can associate other factors with sleep deprivation. For example, the ICU environment itself promotes sleep disruption (*see Table 1*). Peak noise levels in the

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Table 1: Factors Associated with Sleep Deprivation in the ICU

Environmental Factors
- Ambient noise
- Lighting
- Patient care
- Diagnostics
- Medications

Physiologic Factors
- Pain
- Inflammation and inflammatory mediators
- Organ failure
- Stress
- Delirium

ICU have been measured as high as 85 decibels, well above the Environmental Protection Agency's recommended safe levels and higher levels known to result in arousals from sleep. Noise emits from multiple sources, including alarms, staff conversations, televisions, ventilators, pagers, phones, and patients' families. In the few studies that have attempted to link environmental noise to arousal levels, noise was found to be the etiology of sleep disturbance in about a quarter of cases. This suggests that most arousals are not caused by noise but other factors. One such cause is abnormal light exposure. High levels of light (as high as 1000 lux) can result in a disruption of the normal nocturnal secretion of melatonin and the circadian pacemaker. Lack of exposure to natural light during the day also disrupts this normal circadian pattern. Another factor is patient care activities, such as nursing procedures, taking vital signs, lab draws, X-rays, and invasive procedures, which all result in sleep interruption. In one study, the average patient in a medical ICU experienced a mean of 19 patient care interactions per night shift, any one of which could cause arousal from sleep.[5] In addition, patients on mechanical ventilators have very poor quality sleep. These patients experience up to 80 arousals per hour from sleep, or one interruption every 45 seconds.[6] Medications affect sleep quality and architecture as well. Benzodiazepines prolong stage 2 sleep and decrease slow-wave and REM sleep. Propofol, narcotics, beta-blockers, and even quinolone antibiotics have all been reported to disrupt sleep. While these medications often may be necessary, dosage, frequency, and even choice of medications are modifiable elements of care to consider as they relate to sleep and the development of delirium.

While sleep is important, it is only one element to consider in the overall care of the critically ill patient. The underlying illness drives the potential need for frequent monitoring, interventions, and medications. Clinicians know some information regarding attempts to modify these factors. Alternate modes of ventilation have been tried to improve sleep quality with little to no success. In one study, use of dexmedetomidine in mechanically ventilated patients did not improve sleep quality but completely abolished deep REM sleep.[7] Benzodiazepines are known to abolish restorative REM and deep non-REM sleep. One low-risk treatment that may help is melatonin. One small trial of melatonin 10 mg daily resulted in improvement of nocturnal sleep efficiency in critically ill patients.[8]

Attempts also have been made to modify the environment of care to improve sleep quality (*see Table 2*). Use of earplugs is one low-tech attempt to reduce noise that has been associated with a significant reduction in risk of delirium, although it's unclear to what extent this may also affect sleep architecture.[9] In addition, concerted efforts to decrease environmental noise include closing doors, turning off televisions, lowering the volume on medical equipment, and reducing staff-patient interactions. The concept of a period of "quiet time" by bundling these interventions has been studied. For example, a two-hour quiet time with reduced light and sound exposure and minimized patient interrup-

Table 2: Modifications to the Environment of Care to Promote Sleep

- Earplugs
- Eye masks
- Blackout curtains
- Closing doors
- Quiet times (bundling vital signs, labs, and nursing care; turning off the TV; lowering the volume on alarms in the room; and encouraging family to be silent in the room)

tions has been associated with less need for sedation and a trend toward less delirium.[10] This quiet time, however, was very difficult to implement due to the inherent instability of patients and the need for ongoing important patient care interactions.

Quality sleep is a very important component in the treatment plan for critically ill patients. Clinicians must balance the need for optimal sedation and quality sleep against the need for frequent care interventions and monitoring while minimizing delirium. In the past, physicians and nurses have simply assumed patients would not sleep because of a combination of factors, including severity of illness, need for frequent interruptions for patient care, and the noisy environment. Some low-tech, low-cost, low-risk methods are available to improve patients' ability to sleep in the ICU. However, the best thing to do is to transition patients out of the ICU as quickly as possible. For those that require longer stays, perhaps start by introducing a couple of periods of extended quiet time into each patient's day. Bundling vital signs, medication administration, and nursing care around these periods may go a long way toward increasing quality sleep. These likely will incrementally result in improved quality of care, and may also improve physiologic and long-term outcomes. ■

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ABSTRACT & COMMENTARY

Delaying Intubation in Severe Alcohol Withdrawal

By Samuel Nadler, MD, PhD

Critical Care, Pulmonary Medicine, The Polyclinic Madison Center, Seattle; Clinical Instructor, University of Washington, Seattle

Dr. Nadler reports no financial relationships relevant to this field of study.

SYNOPSIS: Delaying intubation until aspiration or cardiopulmonary decompensation did not affect mortality but increased the incidence of pneumonia and length of stay.

SOURCE: Stewart R, Perez R, Musial B, et al. Outcomes of patients with alcohol withdrawal syndrome treated with high-dose sedatives and deferred intubation. *Annals Am Thorac Soc* 2016;13:248-252.

Alcohol withdrawal is a very common cause of hospital admission and complicates many otherwise routine hospitalizations. Catecholamine storm and agitation that requires sedative medication administration characterize this syndrome. However, both the underlying withdrawal and sedative treatments may precipitate aspiration and cardiopulmonary compromise, necessitating endotracheal intubation. The timing of this inherently risky procedure often is based on clinicians' experiences alone. Both premature and delayed intubation may have significant effects on patient outcomes.

This study examined whether delaying intubation led to worsening outcomes. This was a single center, observational, cohort study of 188 patients admitted between 2008 and 2012 with alcohol withdrawal. Per protocol, all patients received continuous infusions of lorazepam (up to 1.2 mg/hour) then titrated to a Clinical Institute Withdrawal Assess-

ment score of 6 or less. Patients could be admitted to either the ICU or floor-level care. The decision to intubate was deferred until clinically apparent aspiration or cardiopulmonary decompensation occurred. Patients were overwhelmingly male (92.6%) with a median age of 50.8 ± 9 years. Most were admitted to the ward (76.1%) with a mean Acute Physiology and Chronic Health Evaluation II (APACHE II) score of 6.2 ± 3.4. In this cohort, 12.8% experienced seizures, 16% were diagnosed with pneumonia, and the mean length of stay was 9.6 ± 11.7 days.

Several variables were statistically different in intubated vs. non-intubated patients. Intubated patients had higher admission APACHE II scores (7.4 vs. 5.9; $P = 0.01$), a higher rate of cirrhosis (10.5% vs. 2.7%; $P = 0.05$), and congestive heart failure (13.2% vs. 1.3%; $P = 0.004$). Interestingly, there was not a statistically significant difference in the history of delirium tremens, ICU admission, or seizure disorder between the two groups. Although there was no difference in overall mortality in intubated vs. non-intubated patients (2.6% vs. 0%), the rate of pneumonia was significantly higher in intubated patients (55.3% vs. 6%; $P < 0.0001$) as was length of stay (14.7 vs. 6 days; $P < 0.0001$). As would be expected, intubated patients required much higher total doses of benzodiazepines (761 vs. 229 mg lorazepam equivalents; $P < 0.001$) and daily doses of benzodiazepines (64.9 vs. 41.7 mg lorazepam equivalents; $P = 0.01$).

■ COMMENTARY

The authors concluded that deferring endotracheal intubation was not associated with excess morbidity or mortality. However, the data reported here paint a more complicated picture. Clearly, if earlier intubation could have prevented aspiration and the development of pneumonia, there would have been a benefit. This study showed certain variables retrospectively were associated with intubation, but these may not prospectively help clinicians understand the optimal timing of intubation. In the study, intubation was associated with pneumonia (odds radio [OR] = 23.54; 95% confidence interval [CI], 7.97-69.46; $P < 0.001$) and APACHE II > 10 (OR = 5.26; 95% CI, 1.79-15.5; $P = 0.003$). Length of stay was significantly longer in intubated patients. Age > 60 years, average benzodiazepine dose > 50 mg, and seizures did not have statistically significant ORs. It is unclear if this is intrinsic to intubation or related to delayed intubation leading to a more complicated hospitalization.

Although no statistical difference occurred for mortality, this study was not powered to detect such a change. Other studies of alcohol withdrawal show similar or higher mortality rates.[1] This study adds to the knowledge base regarding alcohol withdrawal. It remains a prevalent cause of hospital admission and develops during many routine hospital admissions. Treatment of alcohol withdrawal via a protocol with infusions of benzodiazepines even up to 20 mg/hour without intubation until aspiration or cardiopulmonary compromise did not show excess mortality when compared with other studies. However, it is debatable whether there is not excess morbidity in waiting until aspiration occurs before intubation. A prospective, randomized trial of this protocol would better address this question. Furthermore, understanding prospectively the factors associated with intubation may enable higher vigilance in these patients and prompt earlier intubation that may reduce excess morbidity shown in this trial. ■

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ABSTRACT & COMMENTARY

Communication Facilitators Potentially Can Improve Care for the Sickest ICU Patients

By Elaine Chen, MD

Assistant Professor, Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine, Section of Palliative Medicine, Rush University Medical Center, Chicago

Dr. Chen reports no financial relationships relevant to this field of study.

SYNOPSIS: Highly trained communication facilitators who counseled families and met with physicians and nurses were shown to decrease symptoms of depression in family members at six months and decreased ICU length of stay without affecting mortality.

SOURCE: Curtis JR, Treece PD, Nielsen EL, et al. Randomized trial of communication facilitators to reduce family distress and intensity of end-of-life care. *Am J Respir Crit Care Med* 2016;193:154-162.

Studies have shown that interventions designed to improve clinician-family communication in the ICU can lead to better care. This study was a parallel-group, randomized trial of a "communication facilitator" intervention. Researchers trained a nurse and a social worker to act as communication facilitators to improve goals of care discussions in the ICU and improve communication between ICU team and families of critically ill patients.

The study included five ICUs in two hospitals, an academic level I trauma center, and a community-based hospital. Over five years, researchers screened 2,209 patients, of which 488 met eligibility criteria that included such parameters as mechanically ventilated and high Sequential Organ Failure Assessment scores. Additionally, 168 subjects underwent randomization to either intervention or control in a 1:1 ratio. The final analysis included 86 control patients with 137 family members (51%) and 82 intervention patients with 131 family members (49%).

Facilitators received extensive, evidence-based training in clinician-family communication in the ICU. Facilitators interviewed families and summarized concerns to physicians and nurses. Facilitators participated in family conferences and followed up with family after the patient was discharged to acute care.

Symptoms of depression were assessed using Patient Health Questionnaire-9 at baseline, three months, and six months. Symptoms of anxiety were assessed using the Generalized Anxiety Disorder-7 at baseline, three months, and six months. Symptoms of post-traumatic stress disorder (PTSD) were assessed using the PTSD Checklist Civilian Version (PCL) at three and six months.

There were no statistically significant differences in symptoms of anxiety or PTSD between controls or interventions, although at six months the PTSD difference was just short of statistical significance ($P = 0.056$) in favor of the intervention group demonstrating lower PCL scores. There was a statistically significant decrease in symptoms of depression at six months in the intervention group compared with the control group ($P = 0.017$), but not at three months.

There were no differences in ICU mortality (29% in control group vs. 26% in intervention group; $P = 0.615$) or withdrawal of life support among those who died (71.4% in control group vs. 80% in intervention group; $P = 0.737$). However, time to withdrawal of life support was significantly shorter in the intervention group (16.5 days in control group vs. 7.2 days in intervention group; $P = 0.001$). Among survivors, ICU and hospital length of stay (LOS) were similar. Among decedents, both ICU LOS (28.5 days in control group vs. 7.7 days in intervention group; $P = 0.001$) and hospital LOS (31.8 days in control group vs. 8 days in intervention group; $P = 0.001$) were shorter in the intervention group. Total ICU costs were significantly reduced in the intervention group, but only in decedents. However, average ICU costs per day also decreased in the intervention group among both survivors and decedents.

Reductions in ICU and hospital LOS among patients who died suggest that LOS reduction was due to an earlier decision to withdraw life-sustaining treatments. Mortality did not change; withdrawing life support earlier did not lead to increased mortality. In this study, reduced LOS in the intervention group was associated with reduced costs for patients who died, suggesting that reduced intensity of end-of-life care occurred with no worsening, but instead possibly a reduction in family distress.

This study showed that a communication facilitator trained to improve communication between the ICU team and family may be associated with reduced symptoms of depression for family members six months after a patient's ICU stay. There were no significant differences at three months or in symptoms of anxiety or PTSD. The authors concluded that differences in symptoms of depression only can be viewed as exploratory, and further study is warranted. Overall goals of future studies should be to identify the most beneficial and cost-effective interventions to support families of critically ill patients and reduce intensity of non-beneficial care at the end of life.

■ COMMENTARY

There is no doubt that improved communication with families of critically ill patients with a high risk of mortality is beneficial. But how exactly is it beneficial? And how is it best delivered? This study suggests that it improves family distress at six months, but only in depressive symptoms. An earlier study showed that improving communication decreased levels of depression, anxiety, and PTSD three months after a patient died in the ICU.[1]

This study was limited by a small sample size, difficulty recruiting patients, and loss of follow-up. The results in this study may not be generalizable, given that the intervention involved only two facilitators who were highly skilled and extensively trained and took place in two hospitals that have been the venue for multiple palliative care interventions by perhaps the most well-known U.S. research group on palliative care in the critical care setting. The likely pre-

existing high level of communication skills in these ICUs may bias the outcome, decreasing the likelihood of a positive result. Variability in the model of intensive care delivery can also significantly affect communication. Factors such as location, referral base, availability of palliative care, resident or mid-level provider support, number of beds, and whether the unit is open or closed may all contribute, and the level of significance is difficult to measure. Additionally, this study population was relatively racially homogeneous, with more than 80% of family members classified as Caucasian. Racial issues in trust and withdrawal of life support have been controversial, but data from a more heterogeneous population would be interesting and perhaps more generalizable.

Compassionate and thorough communication is an integral part of the practice of medicine, an art that drew many to medicine in the first place. Clinicians should strive to be excellent communicators with families of critically ill patients, knowing that words can make a difference. But if someone else (e.g., a facilitator) is a better communicator or has more time available to discuss complex issues, why not use one? Additionally, cost of care, LOS, and intensity of non-beneficial treatments at the end of life are issues hospital administrators and payors value highly. If interventions can simultaneously improve family outcomes as well as control costs, shouldn't clinicians pursue this solution aggressively? I look forward to future research in this direction. ■

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ABSTRACT & COMMENTARY

Acetazolamide in Mechanically Ventilated Patients with COPD: Is There a Benefit?

By Kathryn Radigan, MD

Attending Physician, Division of Pulmonary and Critical Care, Stroger Hospital of Cook County, Chicago

Dr. Radigan reports no financial relationships relevant to this field of study.

SYNOPSIS: Compared to placebo, the use of acetazolamide in mechanically ventilated patients with COPD does not significantly reduce the duration of mechanical ventilation.

SOURCE: Faisy C, Meziani F, Planquette B, et al. Effect of acetazolamide vs placebo on duration of invasive mechanical ventilation among patients with chronic obstructive pulmonary disease: A randomized clinical trial. *JAMA* 2016;315:480-488.

Although there are no randomized, controlled trials to support its use, acetazolamide is used frequently as a respiratory stimulant in mechanically ventilated patients suffering from COPD and metabolic alkalosis. To determine whether acetazolamide shortens duration of mechanical ventilation in patients with COPD, Faisy et al conducted the DIABOLO study, a randomized, double-blind, multicenter trial from October 2011 to July 2014. Throughout 15 ICUs in France, 382 patients with COPD who were expected to be mechanically ventilated for > 24 hours were randomized to acetazolamide or placebo. Within 48 hours of ICU admission, patients with pure or mixed metabolic alkalosis received IV acetazolamide 500-1000 mg twice daily or placebo for the duration of their ICU stay. The primary outcome was duration of mechanical ventilation. Secondary outcomes were changes in arterial blood gas and respiratory parameters, weaning duration, adverse events, use of noninvasive ventilation after extubation, successful weaning, duration of ICU stay, and ICU mortality. Of the 382 randomized patients, 380 completed the study. There were no significant differences between the acetazolamide group (n = 187) and the placebo group (n = 193) in median duration of mechanical ventilation (-16.0 hours; 95% confidence interval [CI], -36.5 to 4 hours; $P = 0.17$), duration of weaning off mechanical ventilation (-0.9 hours; 95% CI, -4.3 to 1.3 hours; $P = 0.36$), daily changes of minute ventilation (-0.0 L/min; 95% CI, -0.2 to 0.2 L/min; $P = 0.72$), or partial carbon dioxide pressure in arterial blood (-0.3 mmHg; 95% CI, -0.8 to 0.2 mmHg; $P = 0.25$). Compared to placebo, daily changes of serum bicarbonate (between-group difference, -0.8 mEq/L; 95% CI, -1.2 to -0.5 mEq/L; $P < 0.001$) and number of days with metabolic alkalosis (between-group difference, -1; 95% CI, -2 to -1 days; $P < 0.001$) were decreased significantly in the acetazolamide group. Although there is concern that the study may have been underpowered, the use of acetazolamide in mechanically ventilated COPD

patients does not reduce the duration of mechanical ventilation.

■ COMMENTARY

The principal acid-base disturbances in mechanically ventilated COPD patients are often respiratory acidosis and metabolic alkalosis. Although the causes of metabolic alkalosis in these patients often are multifactorial, there is concern that alkalosis may depress cardiac output and/or respiratory drive, alter oxyhemoglobin dissociation, and favor the development of hypokalemia and hypophosphatemia. These factors may lead to prolonged weaning and duration of mechanical ventilation.[1,2]

Acetazolamide, a carbonic anhydrase inhibitor, frequently has been used as a respiratory stimulant in patients with COPD and metabolic alkalosis. The inhibition of renal carbonic anhydrase enzyme leads to decreased serum bicarbonate and arterial pH and increased minute ventilation as a result of stimulation of peripheral and central chemoreceptors.[3] As the drug is relatively safe, with rare occurrences of undesirable effects, it is used often as a respiratory stimulant in mechanically ventilated patients presenting with COPD and metabolic alkalosis but has not been well-studied. Faisy et al showed that despite achieving significant decreases in serum bicarbonate and fewer days of metabolic alkalosis in patients who were randomized to acetazolamide compared to placebo, there was no significant difference in duration of mechanical ventilation. Although there was no statistically significant decrease in length of mechanical ventilation in patients who received acetazolamide, the between-group difference in median duration of mechanical ventilation may be clinically relevant at 16 hours. Unfortunately, the study was powered to detect a 15% difference in invasive mechanical ventilation duration, and the observed median duration of mechanical ventilation was lower in both groups than anticipated for statistical power. If the study was designed to detect a 10% reduction in mechanical ventilation, it is plausible that the study would have reached statistical significance.

Although a difference in ventilator time may have been missed due to unfortunate statistics, it also must be noted that acetazolamide is a drug that features a complex mechanism of action and that its use is often even more complicated in the ICU setting. Although the acetazolamide dose was maximized at 500-1000 mg IV twice daily, it is possible that the dose remained inadequate. To appreciate a clinically relevant respiratory effect, a decrease in serum bicarbonate of at least 5 mEq/L is often necessary. Although serum bicarbonate decreased significantly, it did not affect respiratory parameters. It is unclear whether this decrease in bicarbonate was insufficient to affect respiratory parameters or whether the lack of response was due to tissue compartmentalization of carbonic anhydrase isozymes and low acetazolamide selectivity. Despite the obvious benefit higher doses may have on respiratory drive, it is also important to be wary of increased respiratory drive, especially in patients with COPD, as increased respiratory drive may also lead to increased work of breathing, respiratory muscle fatigue, decreased exhalation time, and possibly placing the patient at increased risk of auto-positive end-expiratory pressure. Furthermore, the authors noted that the PaO_2/FiO_2 ratio of the acetazolamide group was significantly higher than control. It is plausible that if there was a benefit, it may be due to its diuretic effect or the increased oxygen saturation of hemoglobin.

In review of this study, it remains unclear whether acetazolamide is of benefit in mechanically ventilated patients with COPD. Although there was no statistically significant decrease in duration of mechanical ventilation, there was no harm, and patients treated with acetazolamide were found to have increased daily PaO_2/FiO_2 ratio, with a trend toward shorter duration of mechanical ventilation. Therefore, it is the responsibility of clinicians to remain thoughtful regarding the use of acetazolamide in mechanically ventilated patients with COPD and consider its use on a case-by-case basis. ■

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CME/CE QUESTIONS

1. **Mechanically ventilated patients have been documented to have up to how many sleep arousals per hour?**
   a. 10
   b. 20
   c. 40
   d. 60
   e. 80

2. **Which medication improved sleep efficiency in ICU patients in a small study?**
   a. Lorazepam
   b. Dexmedetomidine
   c. Propofol
   d. Melatonin
   e. Levofloxacin

3. **Patients treated for alcohol withdrawal who required intubation were more likely to have:**
   a. cirrhosis.
   b. admission APACHE II score ≥ 10.
   c. congestive heart failure.
   d. All of the above
   e. None of the above

4. **Family members of critically ill patients who met with communication facilitators were shown to have:**
   a. decreased symptoms of anxiety, depression, and post-traumatic stress disorder (PTSD).
   b. decreased symptoms of depression at six months, but no difference in anxiety or PTSD.
   c. increased tendency to withdraw life support.
   d. increased symptoms of anxiety and PTSD.
   e. increased tendency to withdraw life support and decreased symptoms of depression.

5. **A randomized trial of communication facilitators for family members of critically ill patients with a high risk of mortality showed:**
   a. communication facilitators have the potential to reduce the intensity of end-of-life care without increased rates of withdrawal of life support.
   b. there were increased rates of withdrawal of life support among patients with communication facilitators.
   c. communication facilitators have the potential to decrease symptoms of anxiety in family members.
   d. there were no differences in outcomes between patients with and without communication facilitators.
   e. there was increased ICU length of stay among survivors with communication facilitators.

6. **Acetazolamide use in mechanically ventilated COPD patients was associated with significantly decreased:**
   a. in-hospital mortality.
   b. duration of mechanical ventilation.
   c. serum bicarbonate levels.
   d. All of the above
   e. None of the above

CME/CE OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- identify the particular clinical, legal, or scientific issues related to critical care;
- describe how those issues affect physicians, nurses, healthcare workers, hospitals, or the healthcare industry; and
- cite solutions to the problems associated with those issues.