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Critical Care [ALERT]

A monthly update of developments in critical care and intensive care medicine

ABSTRACT & COMMENTARY

How to Use Less Sedation and Improve Outcomes in Mechanically Ventilated Patients

By David J. Pierson, MD, Editor

SYNOPSIS: This was a comprehensive, interdisciplinary, 2-year quality improvement project to reduce continuous sedation infusions and improve the recognition and prevention of delirium in patients with acute lung injury. It resulted in less infusion use, more days per patient without sedation, and more patient days awake and not delirious, although the median proportion of days with delirium per patient actually increased.

SOURCE: Hager DN, et al. Reducing deep sedation and delirium in acute lung injury patients: A quality improvement project. *Crit Care Med* 2013;41:1435-1442.

Hager and colleagues report on a quality improvement (QI) project aimed at decreasing the use of continuous sedative infusions in mechanically ventilated patients, and also at increasing awareness, recognition, prevention, and management of delirium in such patients. To maximize the comparability of the patients and the care they received apart from this intervention in their before- and after-study design, they included only adults with acute lung injury (ALI) managed in a single unit, the medical ICU at Johns Hopkins Hospital. In this unit, case definitions, patient demographics, admission patterns, staffing, and most aspects of patient management (including other protocols) did not change during the 6.5-year study period. After a 30-month control period in which all ALI patients were prospectively enrolled, the investigators carried out a comprehensive, 2-year transition program to elicit staff buy-in and adoption of a new sedation protocol and delirium screening approach, after which they again enrolled all ALI patients for a 20-month post-intervention study period.

Severity of illness, management of mechanical ventilation, and other features of the patients and their care did not vary between the two study periods, according to the comparisons used by the

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Critical Care [ALERT]

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authors. There were 120 patients in the historical control group and 82 patients in the post-intervention group. After implementation of the new sedation protocol, the median proportions of ICU days on which patients received continuous sedative infusions were significantly less: 33% vs 74%, and 22% vs 70%, respectively, for narcotics and benzodiazepines, both $P < 0.001$. In the second period, the median Richmond Agitation Sedation Scale (RASS) score was -1.5, compared with -4.0 in the control period, indicating greater wakefulness ($P < 0.001$), and there was a higher proportion of ICU days per patient without sedation (RASS +1, 0, or -1; 50% vs 20%; $P < 0.001$). In addition, on routine assessment, patients were less often comatose (RASS -4 or -5) in the post-intervention period: 23% vs 65%, $P < 0.001$. However, median days per patient in which delirium was present increased (38% vs 20%, $P < 0.01$) during the post-intervention period. Average daily pain score per patient during the second period was very low at 0.5.

The above results document that the unit-level intervention to decrease sedation in patients with ALI was effective. However, the authors' primary thrust in this article is to describe how they successfully implemented this cultural change in their ICU and successfully increased staff awareness and recognition of delirium. They point out that the observed increase in days of delirium per patient is unsurprising in the context of markedly reduced sedation administration and the prevalence of profound sedation, given that patients typically pass through a stage of delirium as they recover from sedative-induced coma toward normal wakefulness.

To implement their QI project, the authors first developed a new sedation protocol that targeted a RASS score of 0 ("alert and calm," see Table 1) in all ICU patients, including those on mechanical ventilation. The default route of administration for both benzodiazepines (e.g., midazolam) and narcotics (e.g., fentanyl) was to be intermittent dosing, and continuous infusions were to be permitted only if as-needed intermittent administration was inadequate according to specified criteria. Regardless of the route and schedule of administration, all sedatives and narcotics were to be discontinued daily at 8 a.m. Nurses were trained to anticipate agitated delirium at this time as patients awoke, and to tolerate a certain delirium level (RASS +2) for up to 4 hours before resuming intermittent sedation.

It is not surprising that the nurses were initially reluctant to comply with these elements of the protocol. However, Hager and colleagues went to great lengths to achieve buy-in by all staff members, with training in delirium recognition and treatment with both pharmacologic and non-pharmacologic approaches, and this was ultimately successful. The paper describes the QI process in detail. Briefly, the authors used the "4Es" model of Pronovost et al:[2] engage, educate, execute, and evaluate. Engagement was achieved by an interdisciplinary QI team that included intensivists, MICU nurse educators, and pharmacists, with assistance from psychiatrists and a neuropsychologist. The day and night nursing staffs as well as staff and housestaff physicians received extensive training, and "super-users" who were available at all shifts were trained and directly facilitated the implementation of the protocol. The protocol was included in the electronic medical record, and bedside nurses reported each patient's RASS score and delirium status (using the Confusion Assessment Method for ICU,[3] CAM-ICU, see Table 2) during morning rounds. Evaluation of protocol acceptance and adherence by all ICU clinician groups continued on an ongoing basis following its formal implementation. No doubt as a result of this substantial and continuing effort by the interdisciplinary QI team, compliance with the protocol was very good, with at least 90% of scheduled RASS and CAM-ICU assessments being completed in both the control and QI periods.

COMMENTARY

In your ICU, is the need for sedation

Table 1: Assessing Patient Sedation Using the Richmond Agitation-Sedation Scale (RASS)			
Stimulation	Score	Term	Description
None (observation)	+4	Combative	Violent; immediate danger to staff
	+3	Very agitated	Pulls or removes tubes or catheters; aggressive
	+2	Agitated	Frequent non-purposeful movement; fights ventilator
	+1	Restless	Anxious but movements not vigorous or aggressive
	0	Alert and calm	Spontaneously pays attention to caregiver
Voice	-1	Drowsy	Not fully alert but has sustained awakening to voice; maintains eye contact > 10 sec
	-2	Light sedation	Briefly awakens to voice; eyes open and makes eye contact but < 10 sec
	-3	Moderate sedation	Movement or eye opening to voice, but no eye contact
Touch	-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
	-5	Unarousable	No response to either voice or physical stimulation
Adapted from Sessler CN, et al.[1] Available at http://www.mc.vanderbilt.edu/icudelirium/docs/RASS.pdf.			

assessed using "clinical judgment," "experience," and "patient need" rather than by structured, objective assessment such as the RASS?

Are sedatives and narcotics administered to mechanically ventilated patients routinely or "as needed" rather than according to a standardized protocol? Do such patients receive continuous infusions of these drugs rather than intermittent bolus dosing? Are sedative drips and intermittent dosing interrupted at least once each day in all patients receiving them, in order to determine by objective criteria whether they can be discontinued or their dosages substantially reduced? Are all patients in the ICU routinely and specifically evaluated for the presence of delirium?

In past decades, these questions could be thought of as relating to individual clinician preference and/or local practice traditions. Since then, however, they have been subjected to a great deal of clinical research, the results of which are clear and consistent. Administration of sedatives and narcotics to critically ill patients by continuous intravenous infusion results in giving them more drugs, and they remain longer both on the ventilator and in the ICU. The use of

Table 2: Assessing the Patient for Delirium: The Confusion Assessment Method for the ICU (CAM-ICU)			
Step	Category	Result	Delirium Status
1	Acute change or fluctuating course of mental status: • Is there an acute change from mental status baseline? • Has the patient's mental status fluctuated during the past 24 hours?	"No" to both	None
2	(If "yes" to one or both questions in step 1) Inattention: • "Squeeze my hand when I say the letter 'A'" [Read the following letter sequence: S A V E A H A A R T] • Errors: No squeeze with letter "A," and/or squeeze on a letter other than "A"	0-2 errors	None
3	(If > 2 errors on step 2) Altered level of consciousness: • Refer to RASS score	RASS score other than 0	Present (CAM-ICU positive)
4	(If RASS score other than 0) Disorganized thinking: Questions: • Will a stone float on water? • Are there fish in the sea? • Does one pound weigh more than two? • Can you use a hammer to pound a nail? Commands: • "Hold up this many fingers" (Hold up 2 fingers) • "Now do the same thing with the other hand" (Do not demonstrate) • Alternative if patient cannot move both arms: "Add one more finger"	0–1 error > 1 error	None Present (CAM-ICU positive)
Adapted from Ely EW, et al.[3] Also available, along with other related resources, at http://www.mc.vanderbilt.edu/icudelirium/assessment.html.			

standardized, objective assessments of the need for sedation leads to less drug being administered. Surviving patients who received less sedation in the ICU have fewer neuropsychological and other problems in the succeeding months and years. And delirium in the ICU is strongly related both to the amount of sedation received and to a number of important long-term adverse outcomes.

Several measures have been well documented to reduce sedative use in the ICU. These include the use of objective, goal-directed assessment of the need for sedation, such as the RASS; intermittent bolus administration rather than continuous infusion; daily infusion interruption (until the patient awakens, not just moves); and efforts to use analgesics for discomfort rather than sedatives. The problem is not lack of evidence, but how to change long-established routine, clinician attitudes, and other aspects of local ICU culture. This study by Hager et al shows that these things can be changed, but also illustrates how much effort, time, and resources this requires. The finding that patients experienced more days of delirium during the period in which sedation was reduced, despite an overall reduction in the combined endpoint of coma and delirium, suggests that further research is needed to clarify and fine-tune best management in this important area of ICU care. ■

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ABSTRACT & COMMENTARY

Automated Weaning: Smarter Approach or Just Clinician Recalcitrance?

By Richard H. Kallet, MS, RRT, FAARC, FCCM

Director of Quality Assurance, Respiratory Care Services, San Francisco General Hospital

Mr. Kallet reports no financial relationships relevant to this field of study.

SYNOPSIS: In this study, closed-loop, titrated pressure support ventilation was associated with a significantly shorter time course until patients passed a spontaneous breathing trial and were successfully extubated compared to a standardized weaning protocol.

SOURCE: Burns KE, et al. Wean earlier and automatically with new technology (The WEAN study): A multicentre, pilot randomized controlled trial. *Am J Respir Crit Care Med* 2013;187:1203-1211.

This pilot study compared closed-loop pressure support (PS) ventilation to a standard spontaneous breathing trial (SBT) protocol in a multidisciplinary ICU setting. The primary objective was to test clinician adherence to automated weaning vs a clinician-directed weaning protocol, whereas duration of mechanical ventilation and successful extubation were secondary objectives. Eligible study patients required more than 24 hours of mechanical ventilation, and randomization only occurred in those who could tolerate a trial of moderately high PS level (i.e., 15 cm H_2O driving pressure) for 60 minutes. Standard criteria for weaning readiness were used. Patients randomized to automated weaning had PS titrated to maintain a "comfort zone" (i.e., respiratory rate 15-34 breaths/min; minimum tidal volume 300 mL; end-tidal carbon dioxide tension < 55 mmHg). This was achieved by closed-loop evaluation of the respiratory pattern every 2-4 minutes with subsequent PS titration in 2-4 cm H_2O increments until the patient could achieve the comfort zone at a standardized SBT-PS setting of 7 cm H_2O. The standard weaning arm consisted of daily SBTs using traditional settings and modes.

Over a 26-month period, nine participating ICUs enrolled and randomized 97 patients. Baseline characteristics were not different between groups. There was a significantly higher incidence of protocol violations (nearly 2.5 times greater) in the automated weaning group that corresponded with surveys indicating lower acceptance of this approach by both physicians and respiratory care practitioners. Despite these issues, automated weaning was associated with a reduced median time to the first successful SBT (4 vs 1 day, $P < 0.0001$), time to first extubation trial (4.5 vs 3 days, $P = 0.02$), and time to first successful extubation (5 vs 4 days, $P = 0.01$), with fewer tracheostomies (35% vs 16%, $P = 0.04$). Both post-extubation

requirements for noninvasive ventilation (14% vs 8.2%, $P = 0.5$) and extubation failure rate (25.6% vs 18.4%, $P = 0.4$) were not different.

COMMENTARY

What is most striking about this study is that despite passing an SBT at a median of 1 day, automated weaning patients who (theoretically) should have been extubated at that point remained intubated for an additional 2 days. And patients in the protocolized weaning arm required 3 days to pass an SBT. This finding is particularly salient because large, randomized, controlled trials uniformly reported 75-80% of critically ill patients (with similar durations of mechanical ventilation) are able to pass their initial SBT.[1] This finding coincided with a relatively high incidence of protocol noncompliance in both study arms (47 total days; average off-protocol duration of approximately 18-23 hours).

Moreover, poor screening and enrollment performances (7 and 0.4 patients per month, per ICU, respectively) suggest insufficient support for investigators/study coordinators. The success of the ARDSNet studies was in part due to robust National Institutes of Health financial support, which allowed for multiple daily interactions between study personnel and clinicians that facilitated protocol adherence.[2] Regardless of whether algorithms are written or programmed into a ventilator mode, practitioners are reluctant to "trust" anything other than their own judgment. This study underscores the continued "culture war" between traditional clinician-centered vs algorithm-driven practice that likely will impede the pace of progress in improving patient outcomes. Understandably, the high-stakes nature of critical care leads to an unavoidable and often unrecognized emotional bias among those entrusted with safeguarding patient well-being. However, there must be a concerted daily effort among clinicians to examine whether their reaction to either protocolized or automated approaches may be unduly influenced by subjective impressions.

In addition, the higher success of automated weaning suggests that more subtle aspects of weaning may be important in determining outcomes. Transient intolerance of an SBT may occur because of abrupt increases in work, particularly when respiratory muscle weakness or anxiety is present. Perception of loaded breathing (and hence dyspnea) is determined largely by the magnitude in muscle load change relative to muscle strength.[3] Thus, SBTs may be aborted too quickly in some patients who might need marginally more time to adapt to load changes. An unanticipated impact of SBTs is that respiratory care practitioners now frequently have multiple patients who require daily (or twice daily) testing that increasingly is being coordinated with daily sedation interruptions. This increases the demand placed on clinicians to complete their assigned tasks and may inadvertently tax their ability (or patience) to fully assess their patients' responses to SBTs. Therefore, a gradual but constant titration of PS may limit bouts of distress and facilitate weaning in ways that traditional ventilator practices and staffing patterns cannot accommodate. ■

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ABSTRACT & COMMENTARY

Mortality Decline With the Use of a Sepsis Treatment Bundle

By Eric C. Walter, MD, MSc

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

SYNOPSIS: This large, multicenter, quality improvement project showed a dramatic reduction in mortality among patients with severe sepsis or septic shock after implementation of a sepsis treatment bundle.

SOURCE: Miller RR, et al. Multicenter implementation of a severe sepsis and septic shock treatment bundle. *Am J Respir Crit Care Med* 2013; 188:77-82.

Guidelines for the treatment of severe sepsis and septic shock over the last decade have focused on early recognition and rapid, aggressive resuscitative efforts. Implementation of these guidelines has consistently been shown to improve outcomes. However, the relative importance of different elements has been debated. As part of a multicenter quality improvement project, a sepsis treatment bundle was implemented for all patients admitted from the emergency department (ED) to the ICU in 11 hospitals within a single health care system (Intermountain Healthcare).

The sepsis treatment bundle was comprised of seven "resuscitative elements" and four "maintenance elements." The first three resuscitative elements — 1) measuring lactate, 2) blood cultures prior to antibiotic administration, and 3) administration of broad-spectrum antibiotics — had to be completed within 3 hours of ED arrival. The additional resuscitation elements were: 4) administration of fluids of 20-40 mL/kg for hypotension or lactate ≥ 4 mmol/L, 5) administration of vasopressors for hypotension despite appropriate fluid administration, 6) obtaining central venous pressure (CVP) and central venous oxygen saturation ($ScVO_2$) at regular intervals with a goal CVP ≥ 8 cm H_2O and $ScVO_2$ ≥ 70%, and 7) administration of inotropes and/or packed red cells (if hematocrit < 30%) if $ScVO_2$ was < 70% and CVP ≥ 8 cm H_2O. All had to be accomplished within 6 hours of ED admission. The four maintenance elements consisted of 1) mean glucose ≤ 180 mg/dL between 12-24 hours following admission, 2) administration of glucocorticoids for persistent hypotension despite adequate fluid resuscitation, or a high dose of a single vasopressor or requiring more than 1 vasopressor, 3) assessment of drotrecogin alfa eligibility, and 4) use of low tidal volume ventilation (6 mL/kg predicted body weight) if mechanically ventilated.

From 2004-2010, 4329 subjects were diagnosed with severe sepsis or septic shock. All-or-none total bundle compliance increased from 4.9% to 73.4% over the study period, showing that a sepsis treatment bundle could be effectively implemented. Over the same time period, in-hospital mortality declined from 21.2% to 8.7%. Interestingly, the decline in mortality did not appear to be due to 100% bundle adherence, as the same decline in mortality was seen in subjects for whom not all bundle elements were implemented (21.7% to 9.7%). Throughout the study, however, the number of bundle elements successfully achieved per patient steadily increased.

The first three resuscitative elements were applied to all subjects. Additional elements were only applied if subjects were eligible (i.e., one could only be eligible for vasopressors, inotropes/red cell transfusion, glucocorticoids, or lung protective ventilation if one was hypotensive, had low $ScVO_2$, or was intubated). A 100% compliance with the first three elements was associated with ineligibility for inotropes/red cell transfusions, glucocorticoids, and lung protective ventilation. Another way of saying this is that in subjects for whom lactate was measured, blood cultures were drawn prior to antibiotics, and broad-spectrum antibiotics were provided within the first 3 hours of ED arrival were less likely to have persistent hypotension, low $ScVO_2$ or require mechanical ventilation. They were also less likely to die ($P < 0.0001$).

COMMENTARY

The authors should be commended on a tremendous amount of work put forth to implement this quality improvement project across 18 ICUs in 11 hospitals as well as to collate data from more than 4000 patients. The authors show that with an effective collaboration between the ED and ICU, a detailed sepsis treatment bundle can be effectively implemented. They also show that aggressive sepsis treatment should not be restricted to the first 6 hours; it should extend into comprehensive ICU care. The all-or-none measurement bar prevented providers from picking and choosing elements they felt were most beneficial. Supporters will argue that this demanding approach standardized care and led to the impressive decline in mortality. Detractors will argue the extensive bundle was "overkill" and not needed, as mortality declined equally among subjects in whom not all bundle elements were implemented. The truth probably lies somewhere in the middle. Like other pre-post studies evaluating practice changes, the outcome cannot be definitely attributed to the intervention. We may not definitely know what part or parts of the treatment bundle led to the mortality improvement, but clearly the implementation of this bundle achieved a very positive outcome.

The strong association between 100% compliance of the first three resuscitation bundle elements and subsequent severity of illness and death is intriguing. Simply asking physicians to consider sepsis and treat early is vital. Future studies will help delineate the added importance of invasive monitoring, vasopressors, inotropes, and transfusions. In the absence of such studies, these data argue that adherence to most, if not all, sepsis treatment guidelines should be the go-to approach. ■

ABSTRACT & COMMENTARY

Music Therapy Can Reduce Anxiety in Critically Ill Patients

By Leslie A. Hoffman, RN, PhD
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SYNOPSIS: In mechanically ventilated ICU patients, availability of music via headphones resulted in a greater reduction in anxiety and sedation exposure.

SOURCE: Chlan LL, et al. Effects of patient-directed music intervention on anxiety and sedative exposure in critically ill patients receiving mechanical ventilatory support: A randomized clinical trial. *JAMA* 2013;309:2335-2344.

Critically ill, mechanically ventilated patients are known to experience a variety of adverse symptoms, including significant levels of anxiety. Commonly, sedative and analgesic medications are used to manage these symptoms, but they have well-known side effects. The goal of this study was to test whether self-initiated, patient-directed music therapy could reduce anxiety and sedative exposure compared to self-initiated use of noise-canceling headphones or usual care. The subjects were 373 patients admitted to 12 ICUs at five hospitals in the Minneapolis-St. Paul area who were randomized to use of music (n = 126), noise-cancelling headphones (n = 122), or usual care (n = 125). Anxiety was measured using a 100 mm visual analog scale. Daily sedative/analgesic exposure was determined for eight commonly administered medications (midazolam, lorazepam, propofol, dexmedetomidine, morphine, fentanyl, hydromorphone, and haloperidol) using a complicated formula. Subjects in the music group were given a MP3 player, noise-abating headphones, and CD of relaxing music. They were encouraged to listen to music at least twice a day, but were not required to do this. Patients randomized to noise-cancelling headphones were advised to wear the headphones when they wanted to block ICU noise or have quiet time. Patients were followed as long as they received mechanical ventilation or for 30 days.

The sample was 86% white, 52% female, and 59 ± 14 years of age, with an APACHE III score of 63 ± 22. Patients in the music group listened to music 80 ± 126 minutes a day (range, 0-796 minutes). Patients in the noise-cancelling headphones group wore their headphones for 34 ± 90 minutes a day (range, 0-916 minutes). Use of music resulted in a greater reduction in anxiety compared to usual care ($P = 0.003$), but not compared to use of noise-cancelling headphones. Findings in regard to sedation administration were mixed. Music resulted in a greater reduction in frequency of sedation use compared with usual care and noise-cancelling headphones. There was also a greater reduction in sedation amount compared to usual care, but not compared to use of noise-cancelling headphones. On the fifth study day, usual care patients received an average of five doses of one of the eight sedative/analgesic medications compared to three doses for patients in the music group.

COMMENTARY

The important contribution of this study relates to evidence that a non-pharmacological intervention, listening to music via headphones, can reduce self-reported anxiety and sedation administration. The intervention tested was simple to use, inexpensive, and without known side effects, characteristics that are rare when selecting critical care interventions. As noted in an accompanying editorial,[1] there were a number of limitations to this study. When responding to the visual analog scale, patients were asked "how are you feeling today?" Thus, the question may have tapped feelings of global well-being rather than anxiety. The 12 ICUs were not required to use a uniform protocol for sedation administration, so there were likely variations in management. Patients were encouraged, but not required, to use the music and headphones. Some chose not to use them, as evidenced by the substantial variation in use recorded for the music (0-796 min/day) and headphone (0-916 min/day) group. Consequently, the study was a "real-world" test, wherein patients were given the freedom to use or not use the intervention.

Entry criteria required that patients be alert, able to participate in daily care, appropriately follow commands, and cognitively intact with adequately corrected hearing and vision. Patients were excluded if they required vasopressors, were unresponsive or delirious, or had a cognitive

disorder that might interfere with the ability to initiate use of music or the headphones. These criteria omitted a large majority of patients whose care is managed in a high-acuity ICUs.

The subset of patients enrolled in this study were, perhaps, more characteristic of those admitted to a long-term acute care hospital for weaning from prolonged mechanical ventilation or short-stay ICU patients who recover quickly. Mean stay for the total sample was 5.7 ± 6.4 days. These considerations do not detract from the message of the study. For this subset of ICU patients, the study provides convincing evidence that music can be an effective means to reduce anxiety and sedation exposure. ■

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CME/CNE Questions

1. In the QI study of a protocol to reduce sedative and narcotic administration to ventilated patients with acute lung injury, implementation of the protocol resulted in which of the following?

a. No change in route of drug administration, no change in days without sedation, no change in delirium
b. Less continuous drug administration, no change in days without sedation, no change in delirium
c. Less continuous drug administration, more days without sedation, decreased delirium
d. Less continuous drug administration, more days without sedation, increased delirium
e. None of the above

2. Which of the following statements about automated weaning is *false*?

a. Ventilator support is governed by a closed-loop algorithm.
b. Ventilator support is titrated using pressure support ventilation.
c. Pressure support is titrated in steps of 2-4 cm H_2O every 2-4 minutes to maintain a "comfort zone."
d. The comfort zone consists of a respiratory rate between 15-30 and a minimal tidal volume of 300 mL.
e. Ventilator support is titrated using a variable intermittent mandatory rate with a fixed airway pressure.

3. Implementation of a sepsis treatment bundle was associated with:

a. no change in mortality.
b. a reduction in mortality only among patients where 100% adherence to all bundle elements was achieved.
c. a reduction in mortality.
d. a shorter length of ICU stay.
e. less blood product transfusion.

4. When provided the opportunity to listen to music, mechanically ventilated ICU patients:

a. rated anxiety lower when measured using a visual analog scale.
b. infrequently used music and headphones, despite encouragement.
c. preferred applying the headphones without music to cancel ICU noise.
d. rated anxiety lower but used the same amount of sedative drugs.
e. rated anxiety higher but used the same amount of sedative drugs.

CME/CNE 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, health care workers, hospitals, or the health care industry; and
- cite solutions to the problems associated with those issues.

[IN FUTURE ISSUES]

The challenge of breath-stacking during lung-protective ventilation

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

Prostate Medications and Cancer Risks — New Evidence

In this issue: Risk of high-grade prostate cancers; clopidogrel and stroke risk; antibiotics and statins; and FDA actions.

Prostate cancer risk and 5-ARIs

The 5-alpha reductase inhibitors (5-ARI) finasteride (Proscar) and dutasteride (Avodart) are used to treat lower urinary tract symptoms in men. They are known to reduce prostate-specific antigen (PSA) levels and there was hope that they may also reduce the incidence of prostate cancer. But in two large trials, PCPT (finasteride) and REDUCE (dustasteride), despite a nearly 25% reduction in the overall rate of prostate cancer, the risk for high-grade prostate cancers was increased (Gleason score 8-10). Debate has raged for the last several years about the significance of these findings and whether the increase was real or spurious due to detection bias. A new study from Sweden attempts to clarify this issue. Using the National Prostate Cancer Register along with prescription data, nearly 27,000 cases of prostate cancer were identified along with some 134,000 matched controls. More than 7800 men were exposed to a 5-ARI, including 1500 with prostate cancer and 6300 controls. As noted in previous studies, the risk of prostate cancer decreased with increasing duration of use of a 5-ARI. With 3 years of treatment, the risk of prostate cancer was 28% lower in the treatment group (odds ratio [OR], 0.72; 95% confidence interval [CI], 0.59-0.89; $P < 0.001$ for trend). The reduction was seen primarily for Gleason score 2-6 and score 7 tumors ($P < 0.001$ for trend for both). However, as opposed to previous studies, the risk for higher grade tumors was not significantly increased, although the risk was not decreased either. By 3 years, the OR was 1.23 (95% CI, 0.90-1.68; $P = 0.46$ for trend), but did not reach statistical significance. The ORs for shorter exposures were 0.96 for 0-1 year exposure, 1.07 for 1-2 years, and 0.96 for 2-3 years. The authors conclude that men treated with a 5-ARI for lower urinary tract symptoms had a lower risk of prostate cancer with Gleason scores 2-7 and no evidence of increased risk of Gleason score 8-10 of cancers up to 4 years of treatment (*BMJ* 2013;346:f3406). The FDA issued a safety warning in 2011 regarding finasteride and dutasteride and the risk of high-grade prostate cancers and it is unlikely that this study alone will reverse that, but it is reassuring for the millions of men who take these drugs for lower urinary tract symptoms. ■

Clopidogrel could reduce stroke risk

Adding clopidogrel to aspirin in patients with minor stroke or a transient ischemic attack (TIA) may help reduce the risk of stroke within the next 90 days, according to a new study from China. In a randomized, double-blind, placebo-controlled trial, nearly 5200 patients were seen within 24 hours after onset of minor ischemic stroke or high-risk TIA and randomized to a combination of clopidogrel with aspirin or aspirin alone. The combination group was given clopidogrel at an initial dose of 300 mg followed by 75 mg per day for 90 days along with aspirin 75 mg per day for the first 21 days, while the aspirin alone group got placebo plus aspirin 75 mg for 90 days. The primary outcome was stroke (isch-

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emic or hemorrhagic) during 90 days of follow-up in an intention-to-treat analysis. Stroke occurred in 8.2% of the clopidogrel-aspirin group as compared to 11.7% in the aspirin alone group (hazard ratio 0.68; 95% CI, 0.57-0.81; $P < 0.001$). Moderate or severe hemorrhage occurred in seven patients in the clopidogrel-aspirin group and eight in the aspirin alone group. The rate of hemorrhagic stroke was the same (0.3%) in both groups. The authors conclude that among patients with TIA or minor stroke who are seen within the first 24 hours of symptoms, the combination of clopidogrel and aspirin is superior to aspirin alone for reducing the risk of stroke in the next 90 days. The combination does not increase the risk of hemorrhagic stroke or hemorrhage (*N Engl J Med* published online June 26, 2013). An accompanying editorial states that this trial "proves the concept that dual platelet therapy can be more effective than single platelet therapy in preventing early recurrent stroke in patients with acute symptomatic atherothrombosis...," and also shows that dual platelet therapy can be given without excess harm in patients with acute focal brain ischemia. There is slight concern that the results may not apply to non-Chinese patients with different forms of underlying arterial disease (*N Engl J Med* published online June 26, 2013). ■

Antibiotic coprescription and statins

Use caution if you prescribe clarithromycin or erythromycin to patients on statins. Both drugs (but not azithromycin) inhibit cytochrome P450 isoenzyme 3A4, which can increase blood concentrations of statins, especially atorvastatin, simvastatin, and lovastatin. Researchers from Canada looked at the records of continuous statin users who were prescribed clarithromycin (n = 72,591) or erythromycin (n = 3267) with azithromycin use as a comparator (n = 68,478). The risk of hospitalization for rhabdomyolysis within 30 days was the main outcome. Although the absolute risk was low, concomitant use of clarithromycin/erythromycin with atorvastatin, simvastatin, or lovastatin was associated with a higher rate of hospitalization with rhabdomyolysis, especially in those with acute kidney injury. There was also an increase in all-cause mortality when the drugs were combined (absolute risk for rhabdomyolysis 0.02%, with acute kidney disease 1.26%, all-cause mortality 0.25%, relative risks 2.17, 1.78, and 1.56, respectively). These data suggest that coprescription of clarithromycin or erythromycin with a statin that is metabolized by CYP3A4 (atorvastatin, simvastatin, and lovastatin) increases the risk of statin toxicity (*Ann Intern Med* 2013;158:869-876). ■

FDA actions

The FDA has approved paroxetine for the treatment of hot flashes (vasomotor symptoms) associated with menopause. Paroxetine is a selective serotonin reuptake inhibitor (SSRI) and has the same active ingredient in the antidepressant Paxil. It is the first non-hormone based drug approved for this indication. The safety and efficacy of the drug was established in two randomized, double-blind, placebo-controlled trials of 1175 postmenopausal women with moderate-to-severe hot flashes that showed paroxetine was more effective in relieving symptoms than placebo. This new form of paroxetine contains 7.5 mg of the drug and is dosed once daily at bedtime. Paroxetine for depression and other psychiatric indications is dosed at 10-40 mg. All forms of paroxetine carry a boxed warning about increased risk of suicide. There is also concern about reduced effectiveness of tamoxifen if both medications are taken together. Paroxetine 7.5 mg for hot flashes is marketed by Noven Therapeutics as Brisdelle.

The FDA has approved a new formulation of selegiline — a once-daily, orally dissolving tablet — for the treatment of Parkinson's disease (PD) in patients who are losing responsiveness to levodopa/carbidopa. Most PD patients start treatment with levodopa/carbidopa, but for many, the effectiveness wanes with increasing "off" periods during which time symptoms worsen. In clinical trials, the new combination of selegiline reduced "off" periods by an average of 2.2 hours per day compared to 0.6 hours for placebo. The dissolvable tablet uses a new system that delivers more drug at a lower dose. The drug company claims this results in fewer side effects. Selegiline, a monoamine oxidase (MAO) inhibitor, has been available as a generic and also as the branded drugs Eldepryl and Zelapar. Like other MAO inhibitors, it can cause severe, even fatal, reactions if given in combination with certain other drugs including meperidine, tramadol, SSRIs, TCA antidepressants, and the over-the-counter medication dextromethorphan. The new orally dissolving selegiline is marketed by Valeant Pharmaceuticals as Zelapar.

The FDA has approved the TNF blocker golimumab for the treatment of ulcerative colitis. The drug was previously approved to treat rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. The approval for ulcerative colitis was based on two studies of more than 800 patients, one group had failed other treatments and the other group were responders who were evaluated for maintenance. In both groups, golimumab was superior to placebo. Golimumab is marketed by Janssen Biotech as Simponi. ■

Clinical Briefs in Primary Care™

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By Louis Kuritzky, MD

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Continuing Warfarin for Pacemaker/ICD Implantation is Safer Than Bridging

Source: Birnie DH, et al. *N Engl J Med* 2013;368:2084-2093.

The decision process to determine the optimal scheduling of antithrombotic therapy in the perioperative period is complex. The most recent AT9 CHEST guidelines suggest discontinuation of warfarin 5 days prior to pacemaker/implantable cardioverter-defibrillator (PCM-ICD) implantation, complemented with heparin bridging. This method is somewhat unwieldy, expensive, and has not been confirmed by a large, randomized trial as optimizing risk reduction. During transition from warfarin to heparin, an interval of increased risk for thromboembolism occurs in some, and the use of heparin has also been shown to frequently be associated with device-pocket hematoma.

In the Bridge or Continue Coumadin for Device Surgery Randomized Controlled trial, 681 PCM-ICD patients were randomized to continued warfarin or heparin bridging. Patient selection criteria also included high baseline annual thromboembolism risk (≥ 5%). The primary outcome of the trial was incidence of significant device-pocket hematoma (DPH), which can result in prolongation of hospitalization, need to stop anticoagulation, or additional surgery.

There was a dramatic difference in risk for the DPH primary endpoint between subjects continued on warfarin uninterrupted (3.5%) and subjects randomized to heparin bridging (16%). Risk reduction through continuation of warfarin was not associated with any increased incidence of major surgical adversities compared with bridging. Continuation of warfarin, uninterrupted, was associated with more than 80% reduction in risk of DPH compared to bridging, while not compromising other measures of safety. ■

Bariatric Surgery Impact on Cholesterol Metabolism

Source: Benetti A, et al. *Diabetes Care* 2013;36:1443-1447.

Bariatric surgery techniques are often described as restrictive (e.g., gastric banding) or diversionary (e.g., biliointestinal bypass). While diversionary surgery (DIV) is associated with greater weight loss and more rapid metabolic changes than restrictive surgery (RES), the greater simplicity and reversibility of the latter are pertinent in selecting which intervention is preferred.

Although the impact of bariatric surgery on diabetes has been much publicized, the impact of bariatric surgery on cholesterol is less well recognized. To date, most of the favorable impact on cholesterol has been attributed to weight loss. Over the long term, DIV is associated with greater weight loss than RES. However, since DIV and RES are associated with similar overall weight loss during the first postoperative 6 months, one could compare cholesterol metabolism of the two types of surgery independent of weight loss.

Benetti et al compared cholesterol metabolism in DIV with RES (n = 20). They found that with DIV, reduced cholesterol absorption produced a decrease in LDL and non-HDL, associated with enhanced catabolic LDL receptor activity in the liver.

Because metabolic changes in both groups in reference to glucose, insulin, insulin resistance, and weight loss were similar, the authors suggest that these favorable cholesterol metabolic changes are induced specifically with DIV, and because weight loss over the specified interval was essentially equivalent, the changes in lipids are not fully explained by weight loss. ■

The Do-it-Yourself Diabetes Diagnosis Kit

Source: Bethel MA, et al. *Diabetes Care* 2013;36:1483-1488.

In the last decade, the threshold for diagnosis of diabetes has expanded to lower levels of fasting glucose, inclusion of reference laboratory A1c, and refinement of the definitions of prediabetes. Use of the oral glucose tolerance test (OGTT) appears to be less and less necessary, considering the relative convenience of other diagnostic tests. Could a self-administered OGTT change the balance and be a positive addition to the diagnostic portfolio?

Bethel et al report on a self-administered OGTT home use kit (SmartGRA) used by 30 diabetic and non-diabetic subjects. The kit includes instructions to guide the user through the process of timed capillary glucose measurement as well as a wireless data recorder for glucose levels, the results of which are *not* visible to the user (glucose measurements are wirelessly transmitted to the clinic for evaluation).

Was self OGTT accurate? In a word,

yes. Comparison of OGTT reports generated by SmartGRA vs office-based testing found comparable reproducibility of results. Although the results of home OGTT tended to overestimate glucose levels compared to the reference laboratory, this emerged as a problem with device calibration, which should be able to be remediated. Overall, subjects found the device easy to use.

As a proof-of-concept trial, these results lend credence to the idea that OGTT — generally conceded to be sufficiently unwieldy so that other diagnostic tests are preferred — might merit reconsideration if a well-calibrated, similarly patient-friendly device comes to market. ■

Low Creatinine Excretion Associated with Mortality in Type 2 Diabetes

Source: Sinkeler SJ, et al. *Diabetes Care* 2013;36:1489-1494.

Creatinine excretion (CER), as measured by the 24-hour urinary excretion of creatinine, has recently been noted to be associated with increased mortality, both in persons with underlying renal disease and the general population. CER reflects overall lean muscle mass, so that declines in CER may simply reflect deconditioning, loss of muscle mass, cachexia, malnutrition, etc., each of which may have a negative impact on mortality.

Sinkeler et al report on data accrued from two previously completed trials of angiotensin receptor blockers in diabetic nephropathy: Reduction of Endpoints in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan trial and the Irbesartan Diabetic Nephropathy trial. Twenty-four hour urinary CER was measured at baseline for the majority (n = 2360) of participants. Since mortality data from both trials are available, the relationship between CER and mortality can be evaluated.

Across the population studied, each halving decrement of CER was associated with a doubling of mortality risk. Since the primary association of CER is with muscle mass, the authors pose the interesting question of whether efforts expended to improve muscle mass, such as enhanced exercise and nutrition, might favorably effect mortality in this population. ■

Diabetes and Cognitive Function

Source: Spauwen PJJ, et al. *Diabetes Care* 2013;36:1554-1561.

The relationship between vascular disease and type 2 diabetes is consistent: Risk for microvascular events (retinopathy, neuropathy, and nephropathy) and macrovascular events (stroke and MI) is increased compared to non-diabetics. Additionally, when diabetics suffer macrovascular events, the consequences are typically more severe than similar events in non-diabetics.

The etiology of cognitive impairment is often multifactorial, including vascular insufficiency. Diabetics have a higher prevalence of cognitive impairment than non-diabetics, but the rate of cognitive decline in diabetics has not been studied.

The Maastricht Aging Study is comprised of 10,396 adults residing in the province of Limburg, the Netherlands. A sample from this population (n = 1290) underwent extensive neuropsychological testing at baseline, 6 years, and 12 years. At baseline, approximately 5% of the population had type 2 diabetes, with an incidence of an additional 5% over subsequent 6-year intervals.

When compared with controls, diabetics had a significant rate of cognitive decline over 6 and 12 years. Even when adjusted for variables that are more commonly comorbid in diabetics (hypertension, dyslipidemia, obesity), the acceleration in cognitive decline was greater in diabetics. As might be intuitive, diabetics with baseline cognitive impairment progressed at a more rapid rate than those without. Whether any specific intervention among diabetics (e.g., better control of glucose, lipids, blood pressure) might ameliorate the exaggerated rate of cognitive decline remains to be determined. ■

Benefits of Screening for Lung Cancer with Low-Dose CT

Source: The National Lung Screening Trial Research Team. *N Engl J Med* 2013;368:1980-1991.

Lung cancer (LCA) is responsible for more deaths than any other cancer worldwide. The burgeoning growth of smoking in developing countries suggests that this dismaying fact is unlikely to diminish in the foreseeable future. Clinical trials of screening for LCA through chest x-ray (CXR) did not show improved outcomes, likely because of its relatively poor discriminative ability in early disease.

The National Lung Screening Trial enrolled smokers and ex-smokers with at least a 30 pack-year history. Participants were randomized to an annual low-dose CT × 3 (n = 26,714) or standard chest x-ray (n = 26,035).

A positive radiographic finding on at least screening was seen in three times as many CT screenees as chest x-ray (27.3% vs 9.2%). LCA was diagnosed in 1.1% of the CT group vs 0.7% in the CXR group.

Screening for LCA was found to reduce LCA-related mortality by 20% and all-cause mortality by 7%.

Most of the abnormalities detected by low-dose CT screening were benign, so that the positive-predictive value for a positive CT was only 3.8% (i.e., about 4% of study subjects with any positive suspicious finding on CT turned out to have LCA). Reassuringly, repeatedly negative low-dose CT had a negative predictive value of 99.9% (i.e., essentially no one who had negative sequential CT screening was diagnosed with LCA during the screening and follow-up period). ■

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